

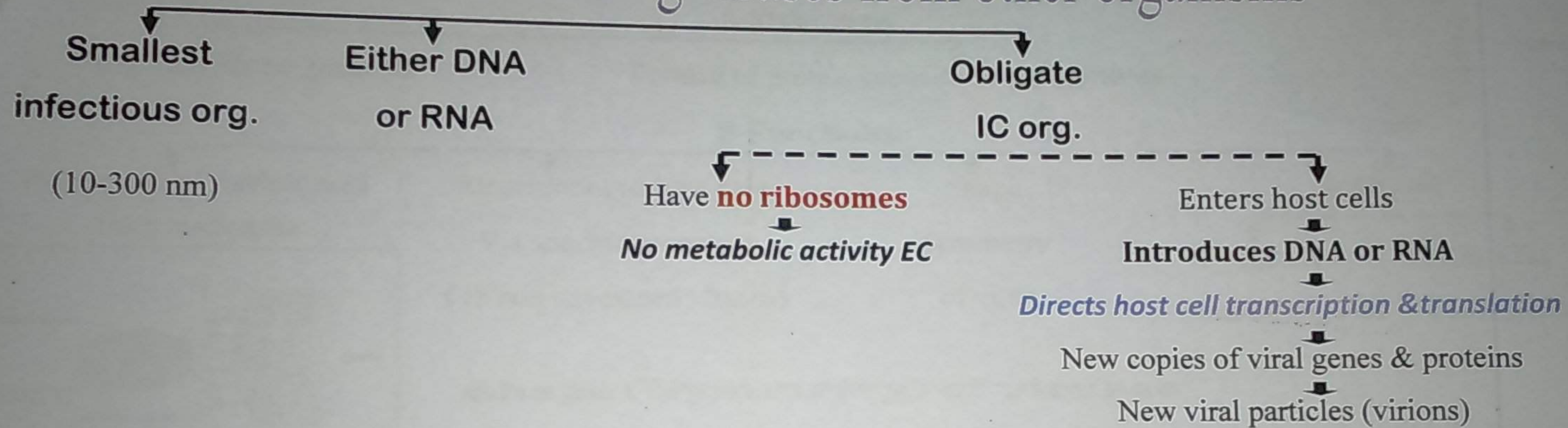
# **Virology 1**

**Basic virology**

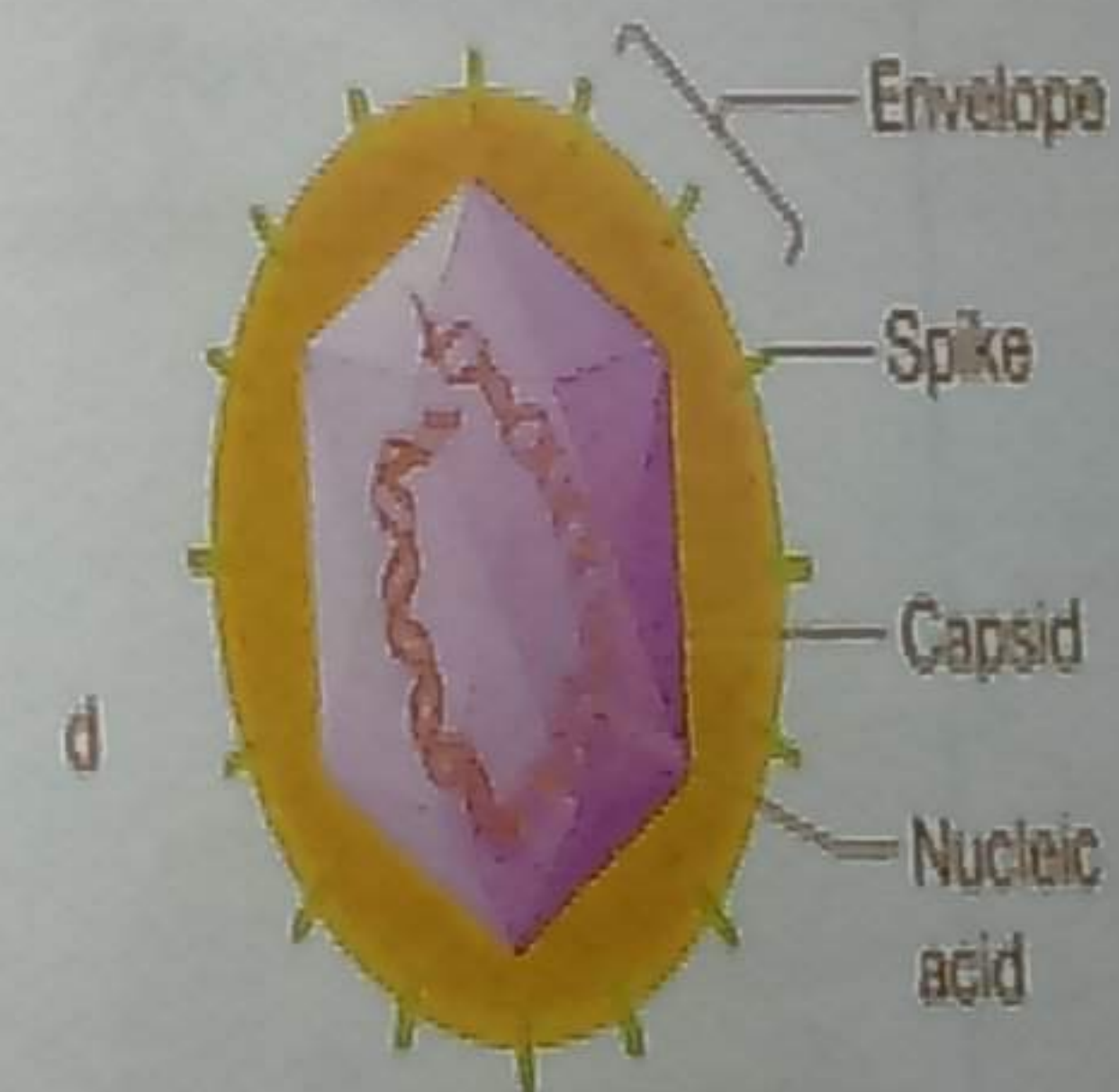
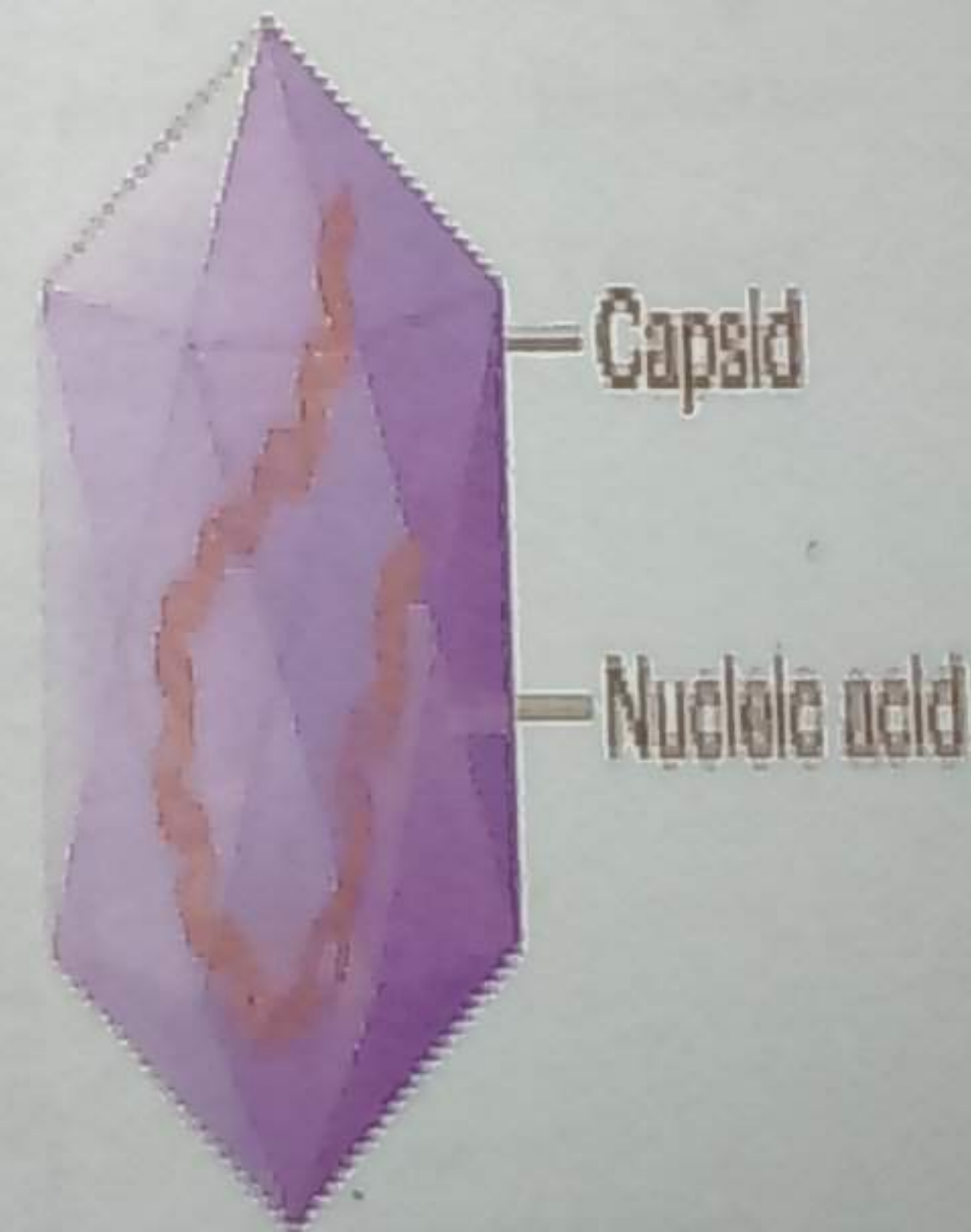
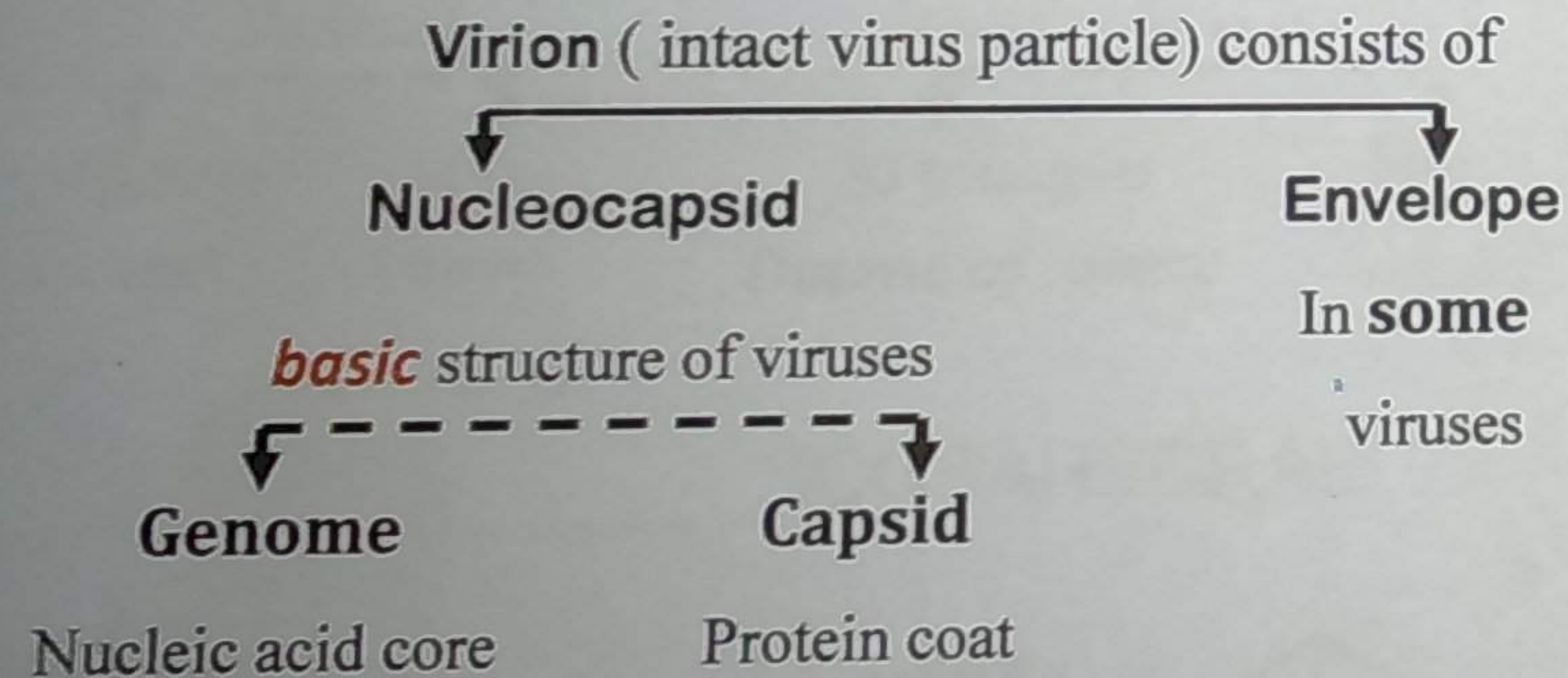
Basic virology



# Properties differentiating viruses from other organisms



## Structure of virus



(b) Enveloped virus

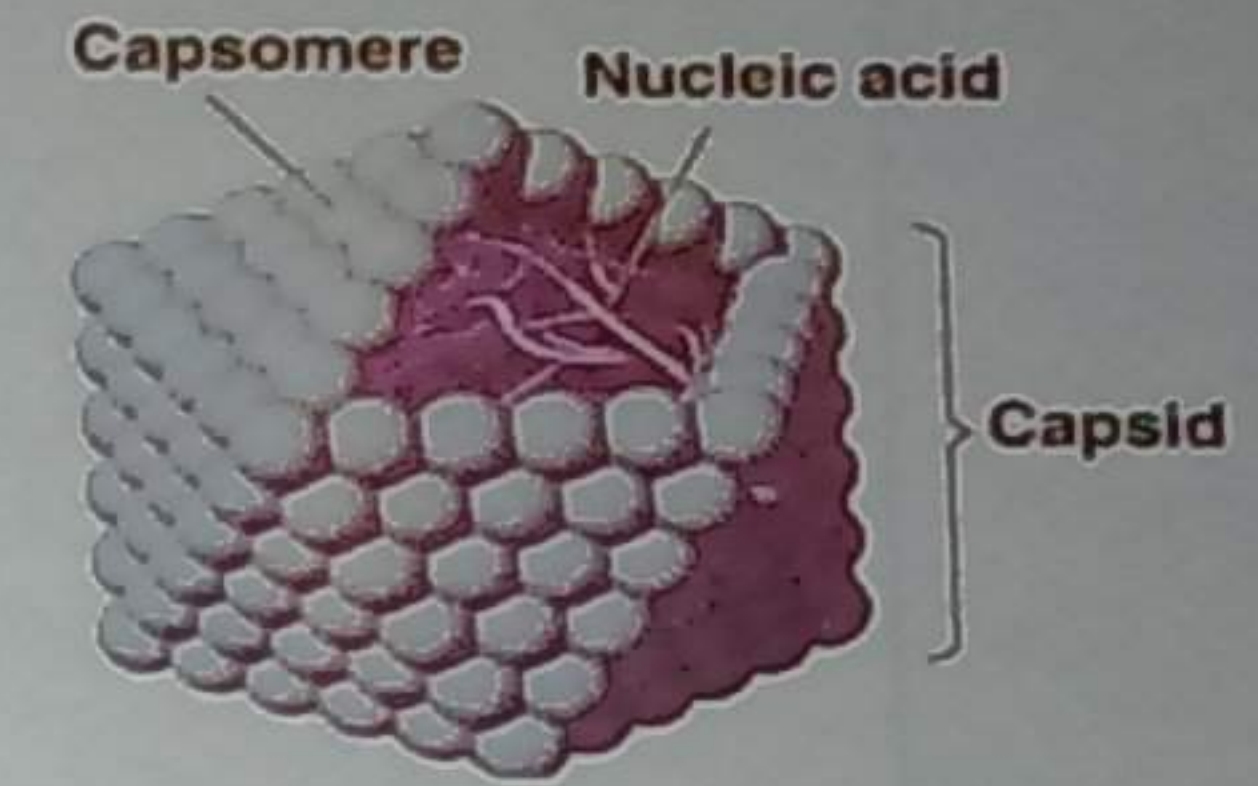


# I - Capsid ( protein coat )

## A-Structure

Encloses genome

Formed of protein subunits called **capsomeres**



## B-Functions

**Protection** of nucleic acid from **nucleases**

**Attachment** to host cells

Via **specific receptors**  
( in non enveloped viruses )

**Shape**

**Symmetry**  
of virus

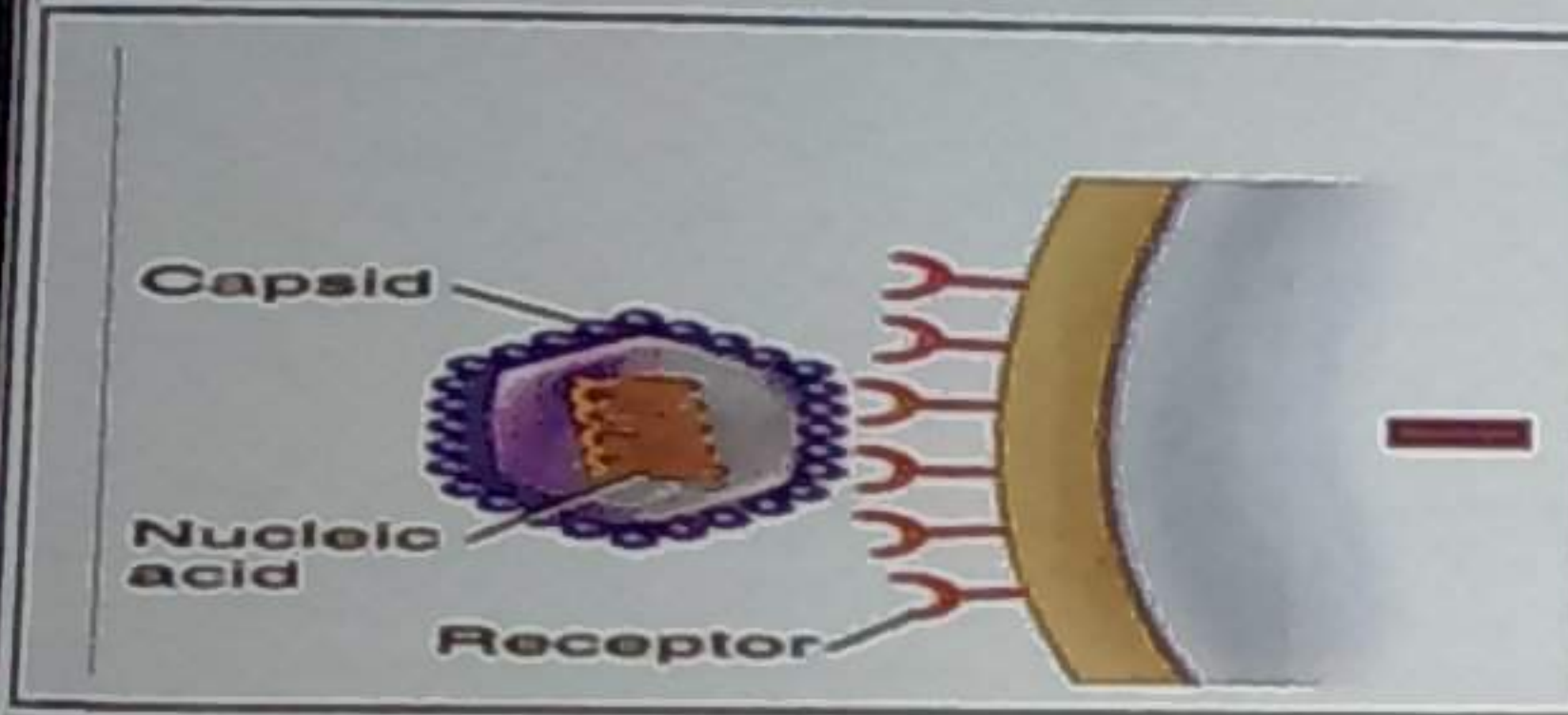
**Antigenic**

Induce

**neutralizing Abs**

⊕ **CTLs**

Kill VICs



## Shape (Symmetry) of viruses

According to arrangement of capsomeres in capsid

**Helical**

Hollow  
**coil**

Myxo  
viruses

**Icosahedral (cubic)**

20 triangles

**Outline of sphere**

Most  
viruses

**Sperm like**

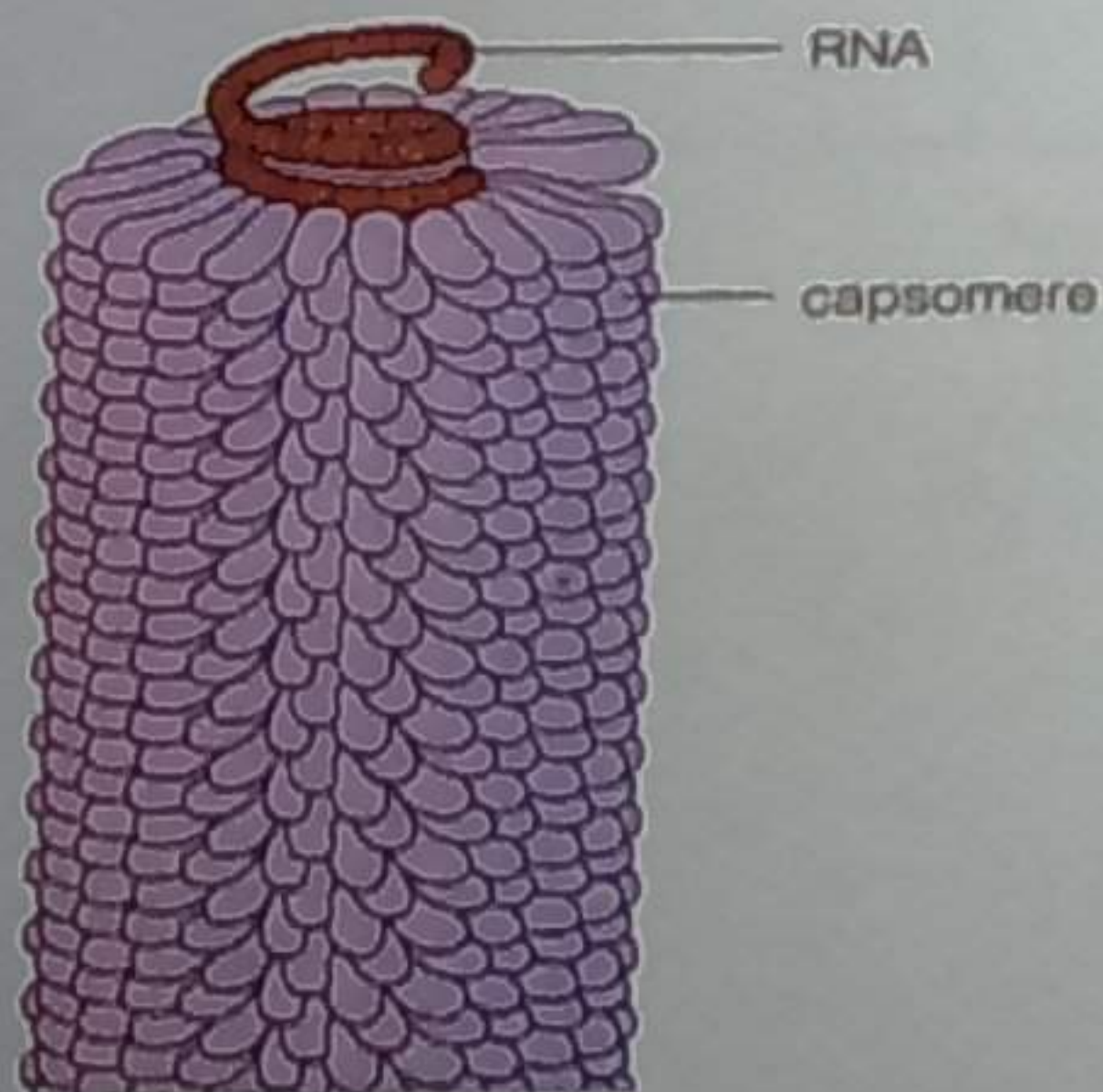
**Head & tail**

Bacterio-  
phages

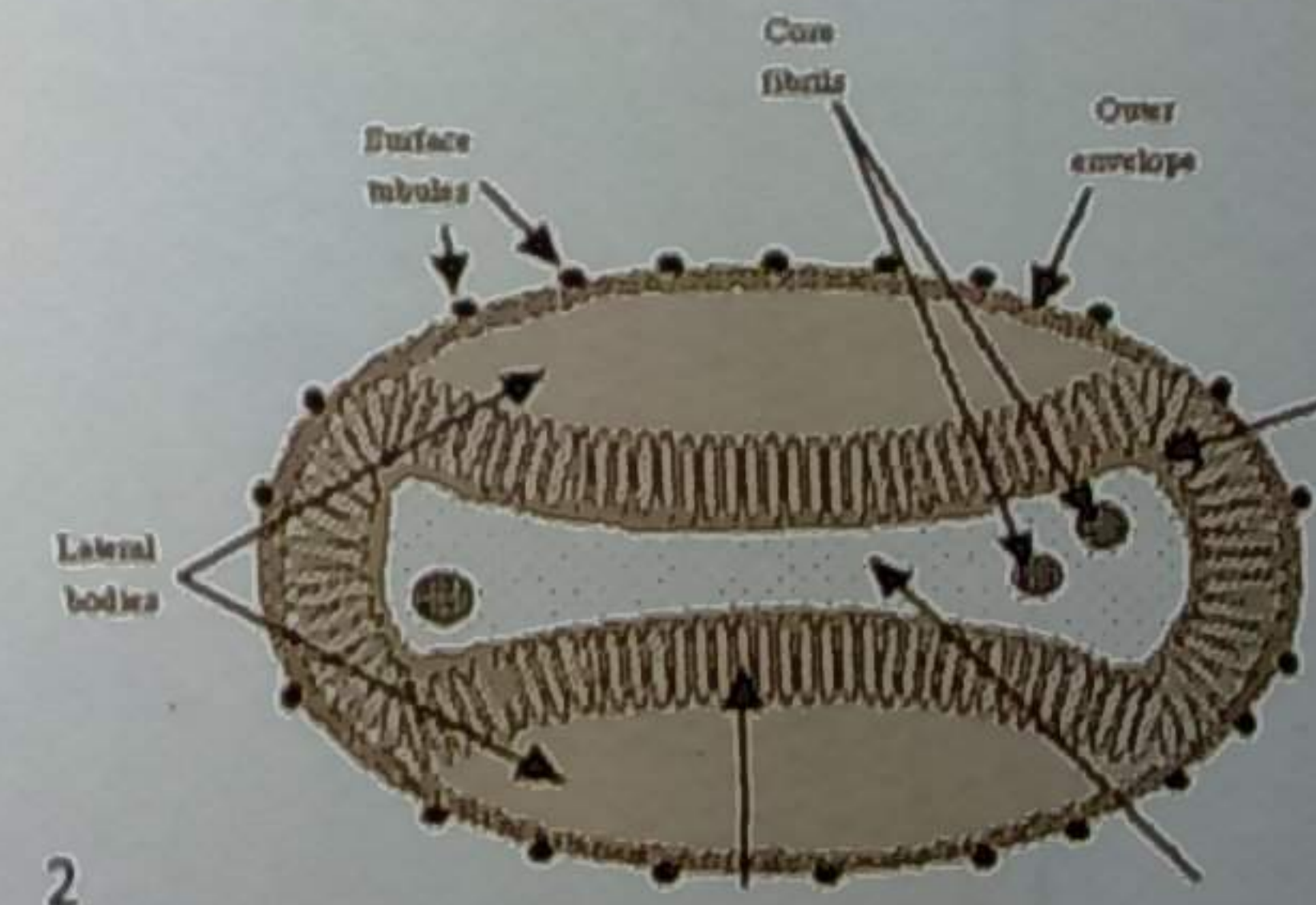
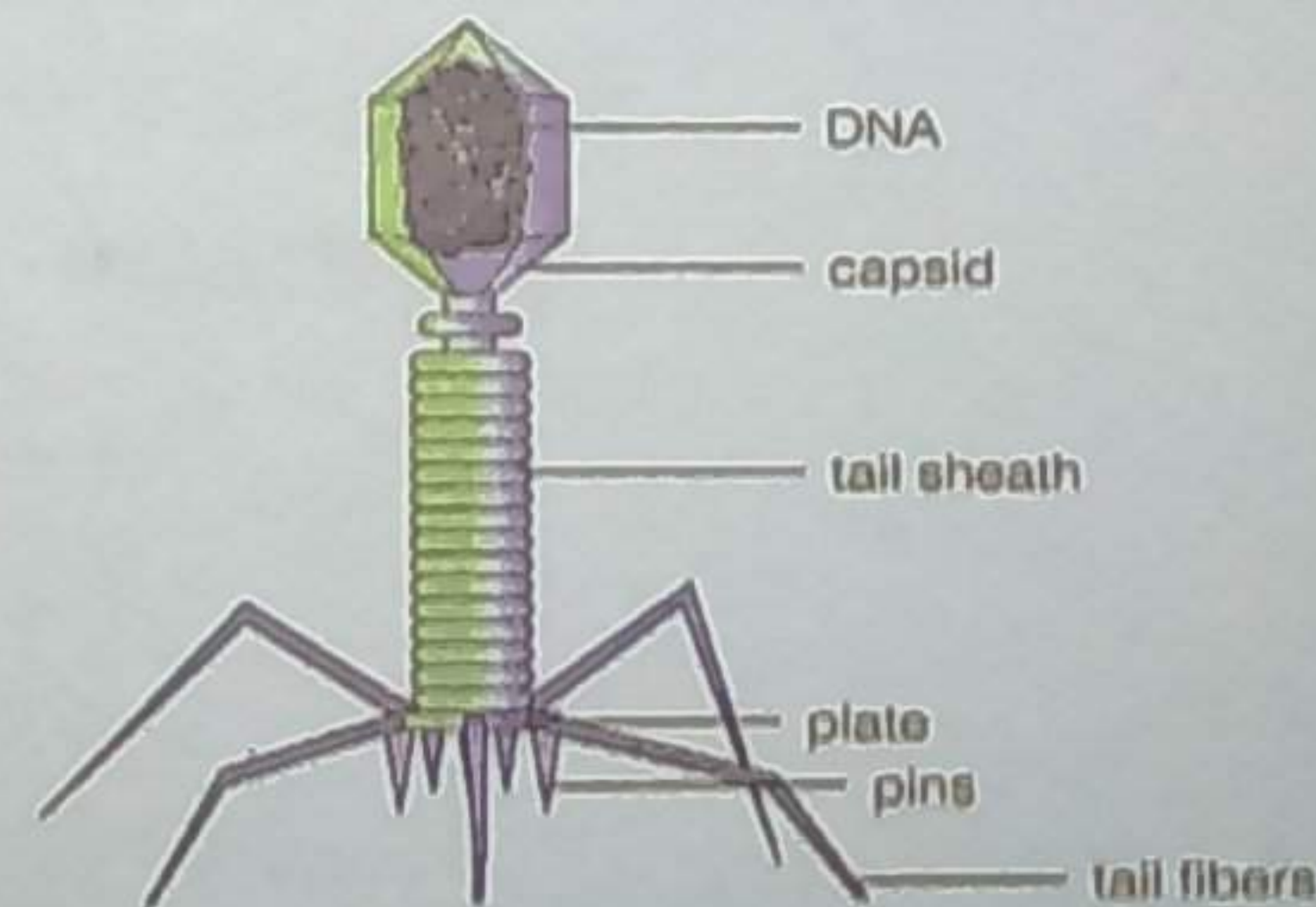
**Complex**

**More complicated**

Pox  
virus

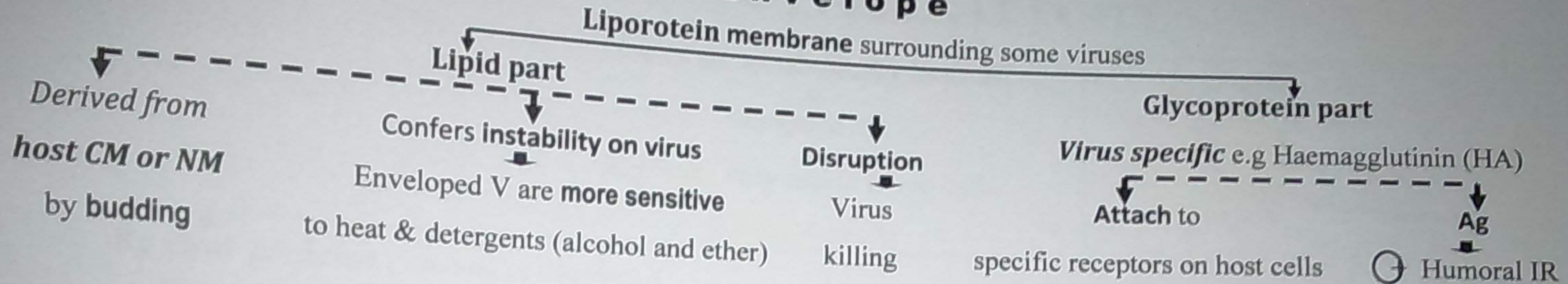


## ICOSAHDRAL





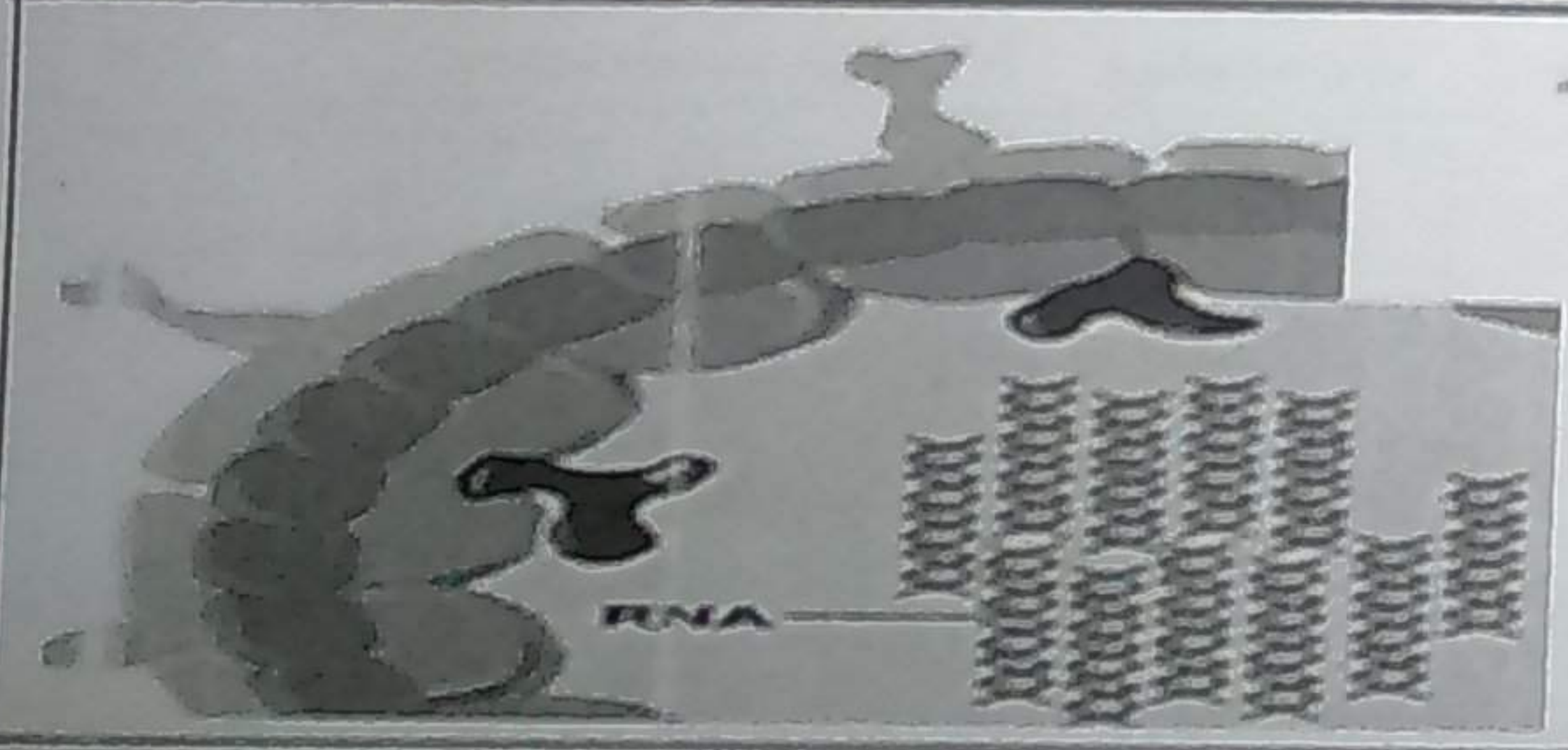
## II - Envelope



## III-Genome ( Nucleic acid core )

### A-Classification

RNA viruses				DNA viruses	
All are SS except Reoviruses  (Rota V)	All are non segmented except: ♦ Bunya ♦ Rota V ♦ Influenza V	Types		All are DS except Parvo viruses	All are non segmented
		+ve sense RNA is <i>Infectious</i> ↓ acts as mRNA in infected cell	-ve sense RNA <i>Isn't Infectious</i> ↓ Transcription by viral RNA polymerase mRNA		



### B-Functions Infectivity

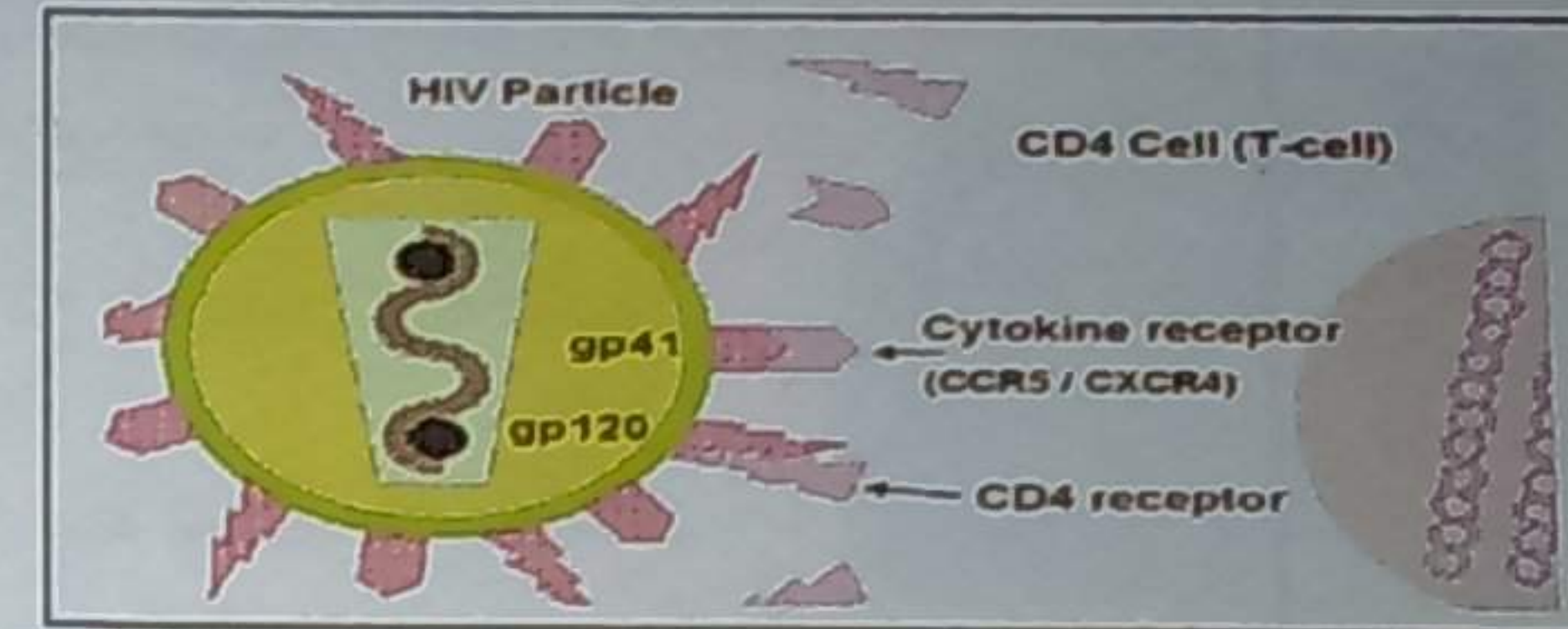


# Viral replication

Viruses are metabolically *inert EC*

*Obligate IC*

Replicate only inside living cells



## 1-Attachment

By viral proteins (on coat or envelope)  
to *specific* host cell *receptors*

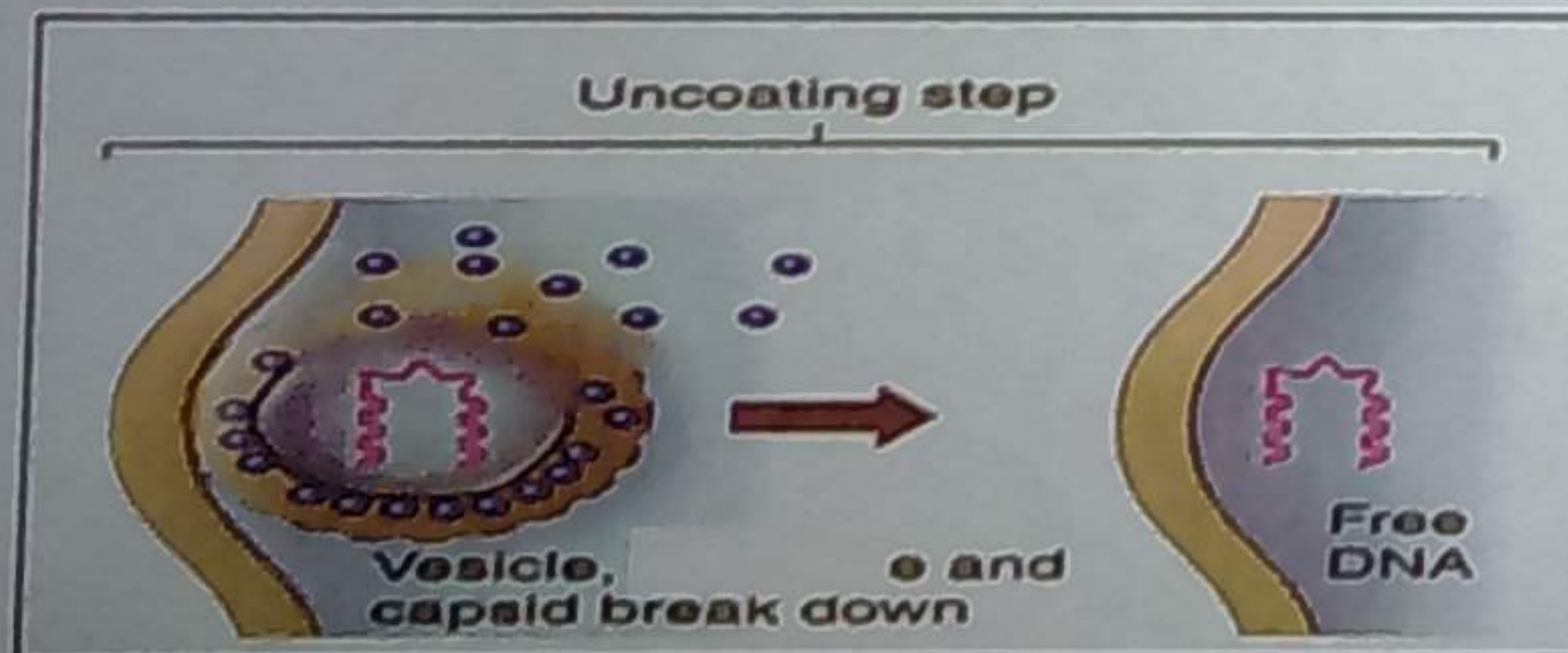
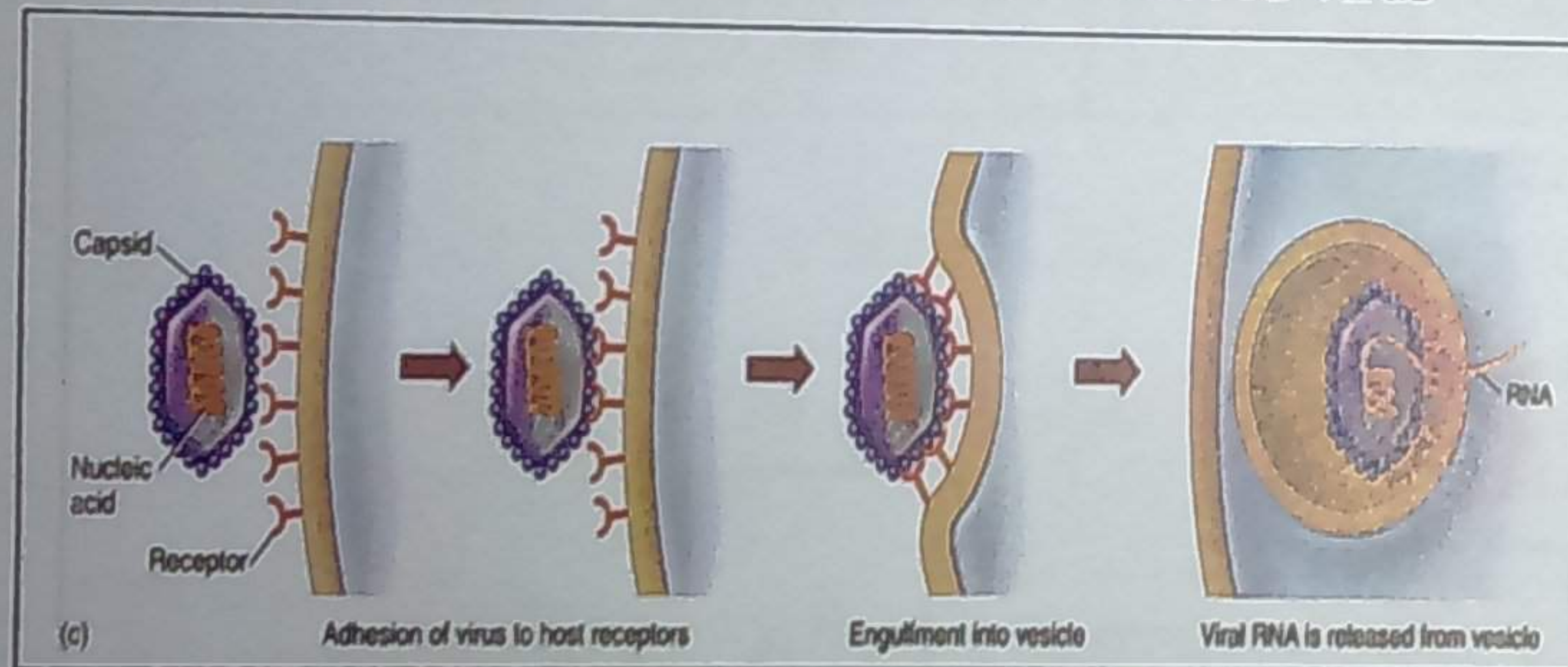
Example

GP 120 on HIV attaches to CD4 (receptor on T cells)

## 2-Penetration

**Endocytosis** (in non enveloped V)

CM invaginates around the adsorbed virus



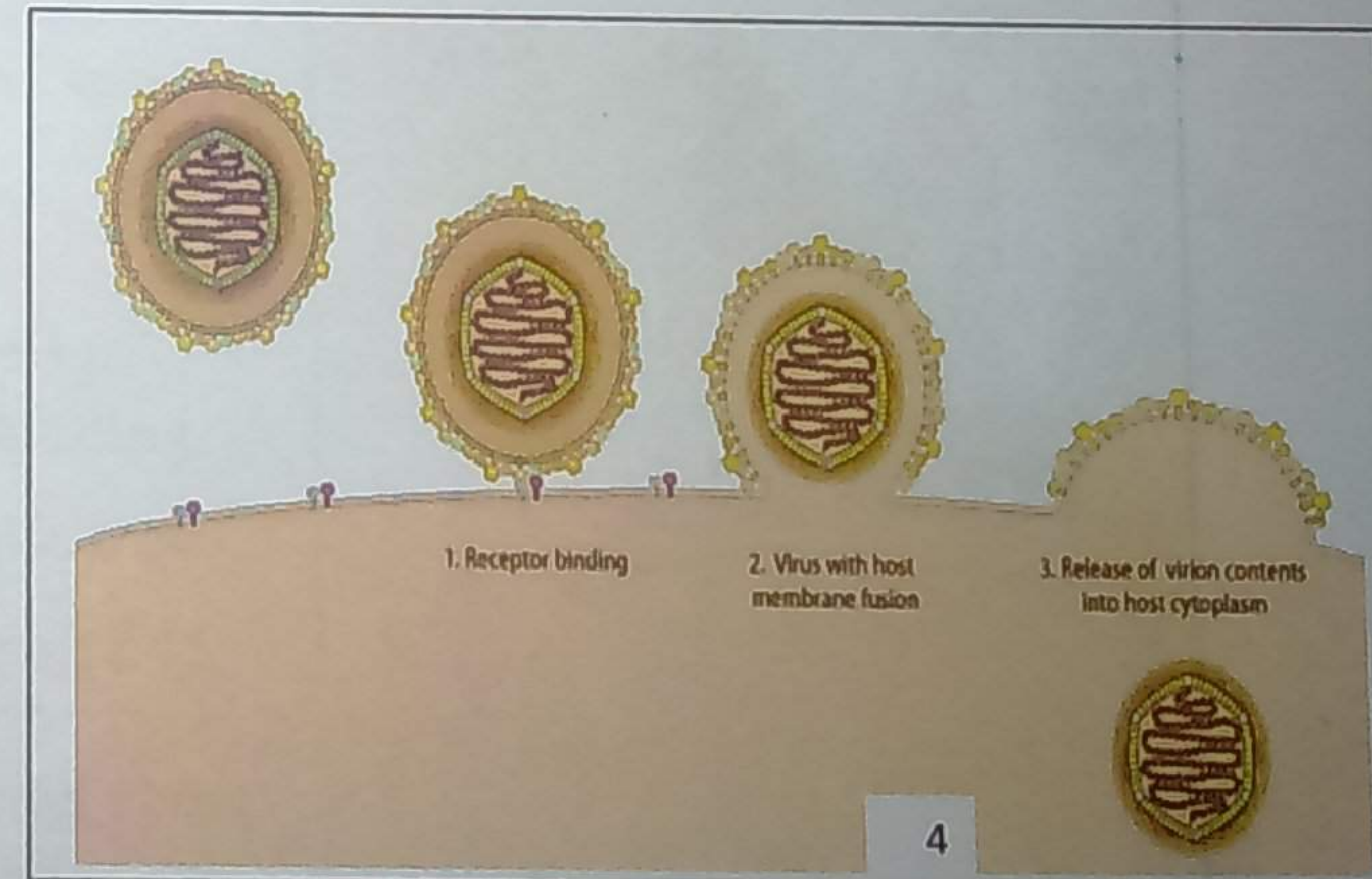
## 3-Uncoating

Host cell *lysosomes*  
remove viral capsid

**Fusion** (in enveloped V)

Between envelope & host CM

Naked nucleocapsid is released into cytoplasm





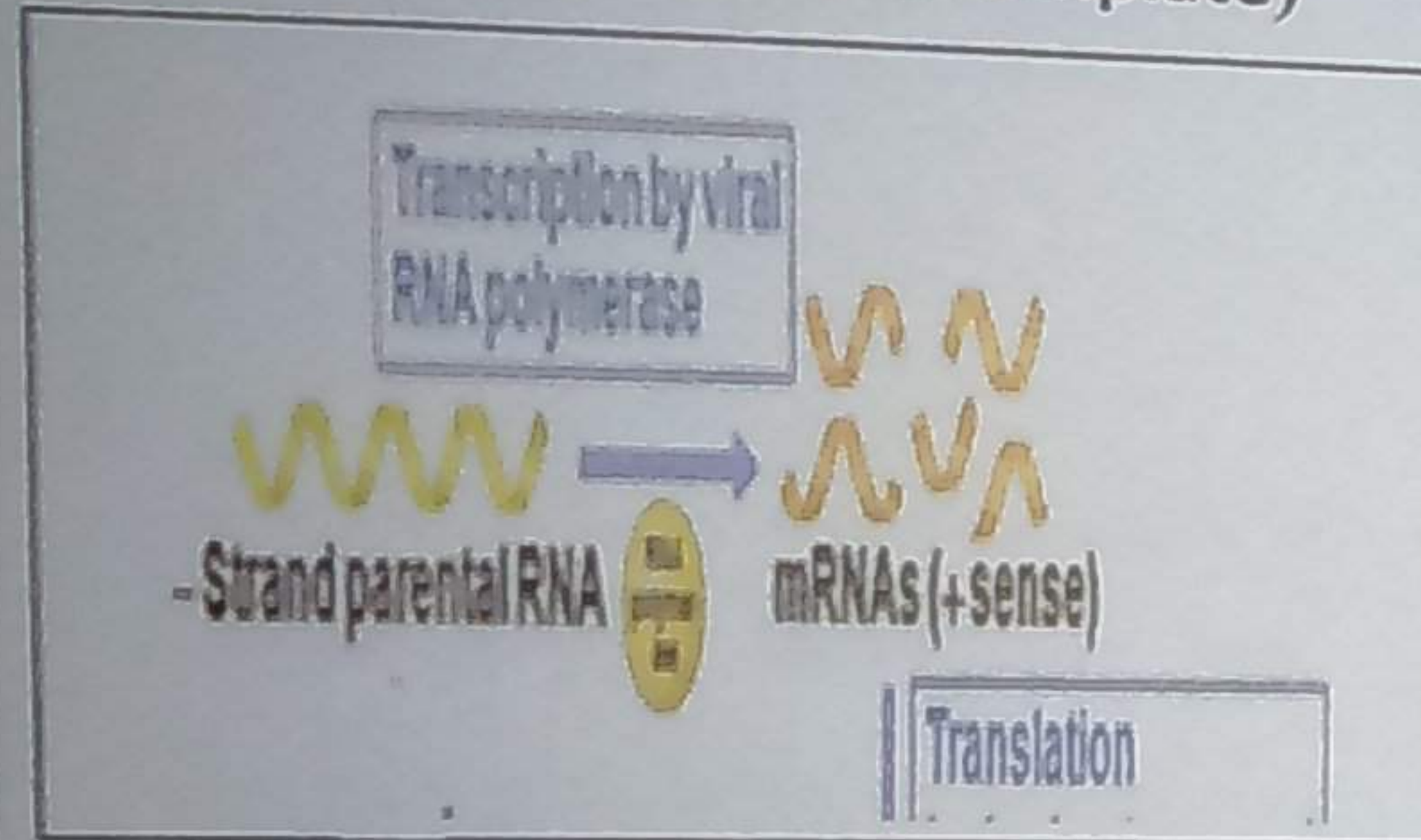
## 4- Synthesis

Called **eclipse** : no viral particles are detected in host cell

### Transcription

-ve sense

Production of viral mRNA (by VRP)  
(Using viral genome as template)



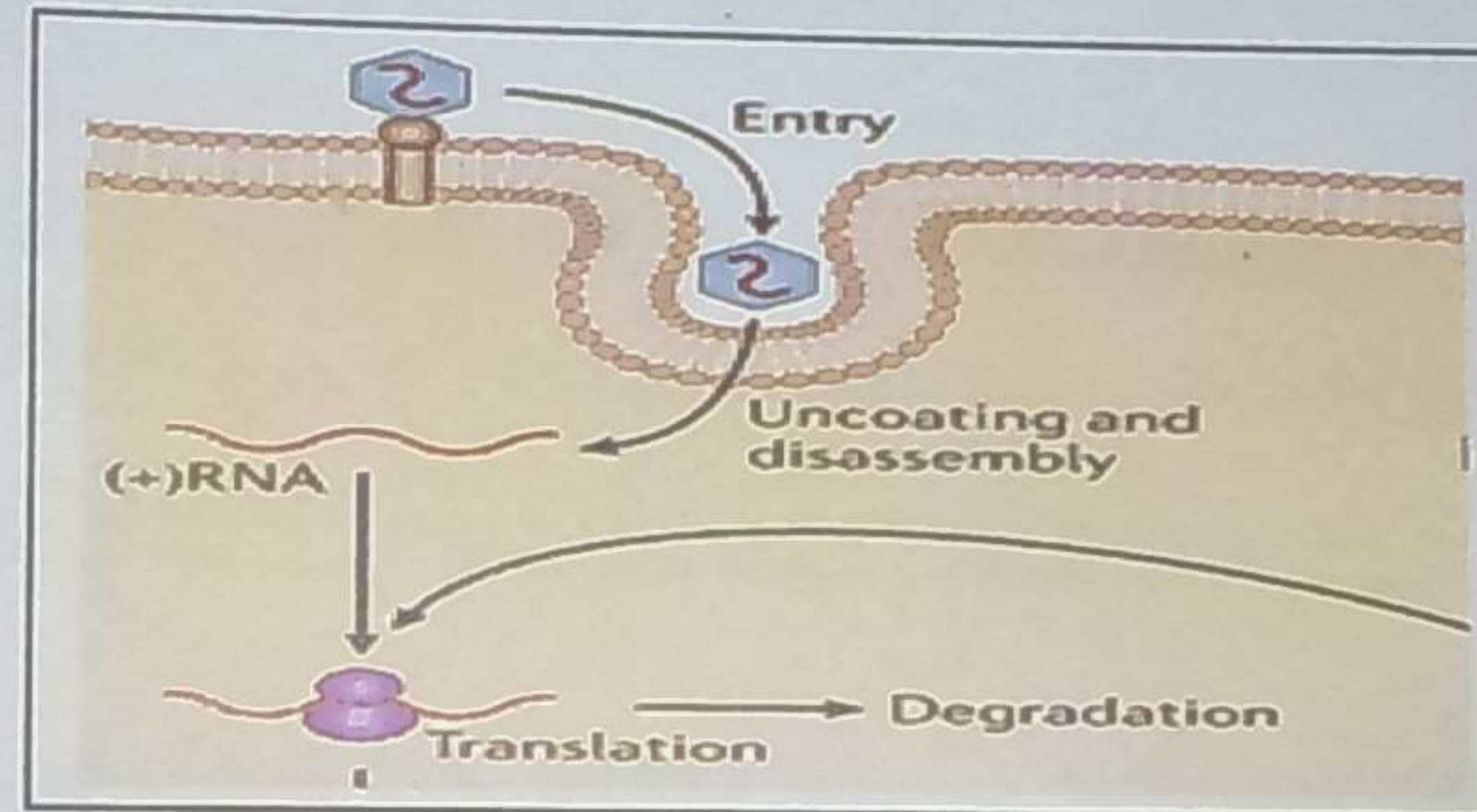
+ve sense

Genome itself acts  
as mRNA

### Translation

mRNA attaches to host ribosomes

Directs synthesis of viral proteins



### Replication of nucleic acids

## 5-Assembly

New nucleic acids & structural proteins assemble  
new virus progeny

## 6-Release

### Rupture of cell

(cytolysis)

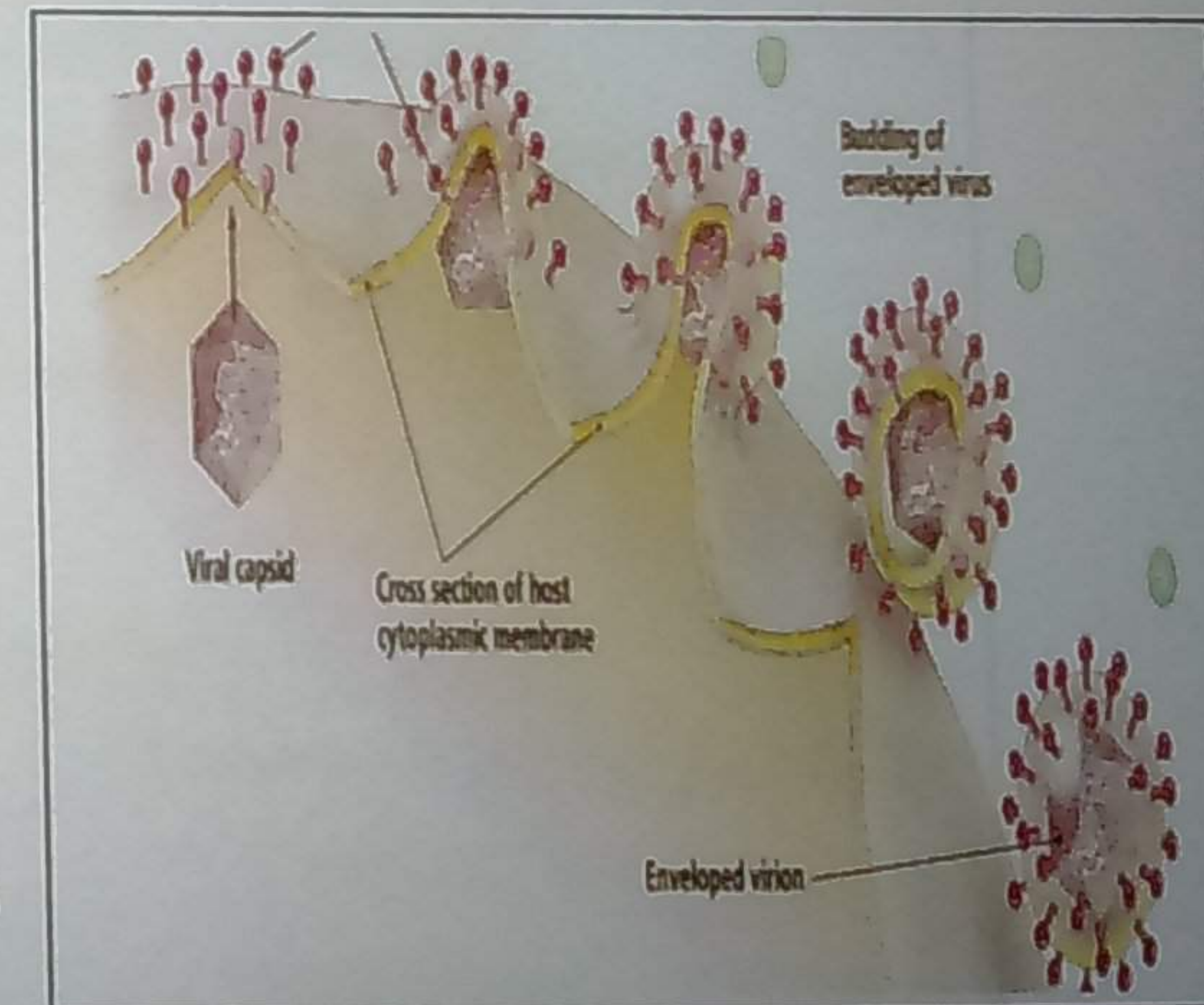
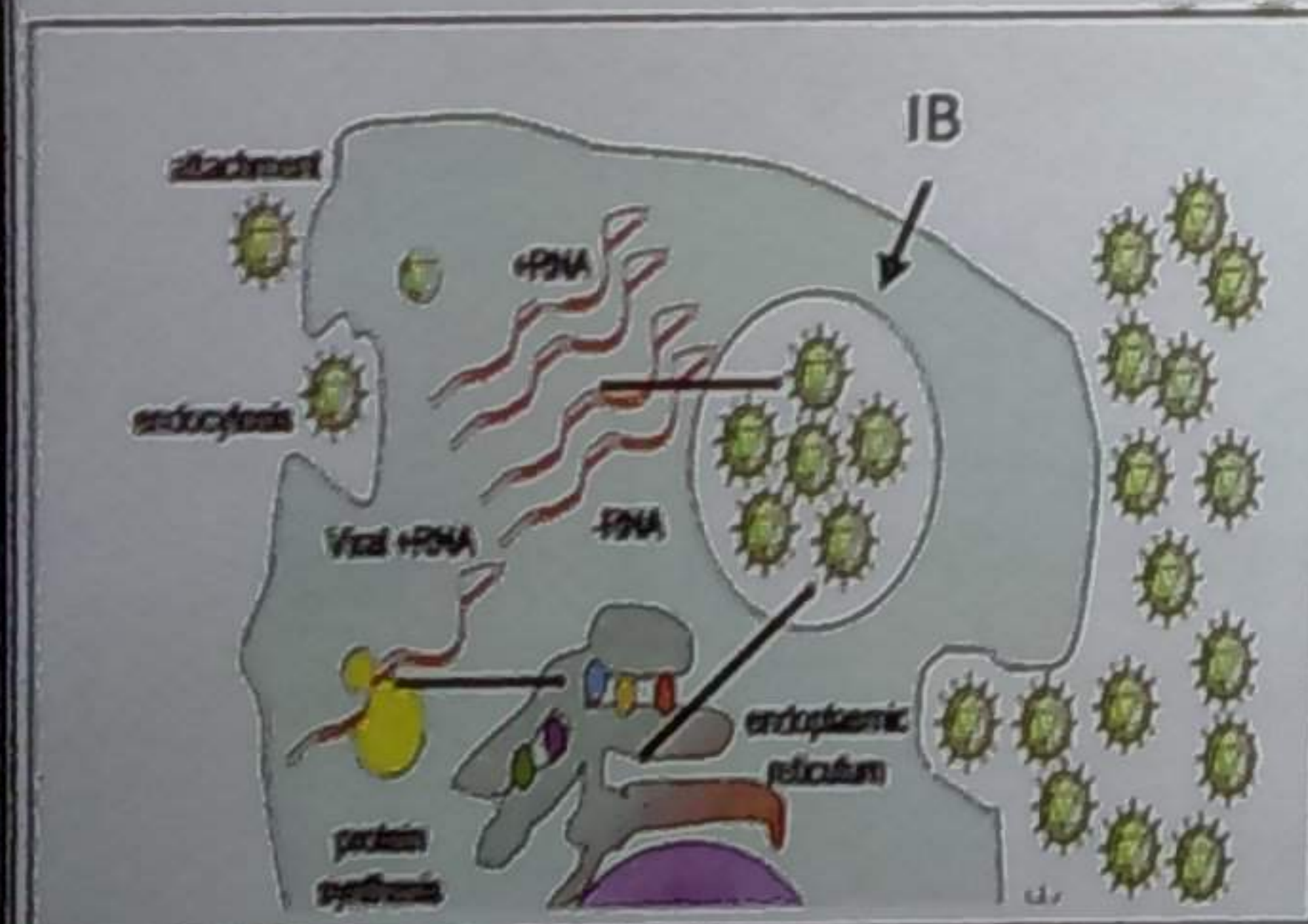
**Non enveloped**

viruses

### Budding

(gradual extrusion  
through CM)

**Enveloped** viruses

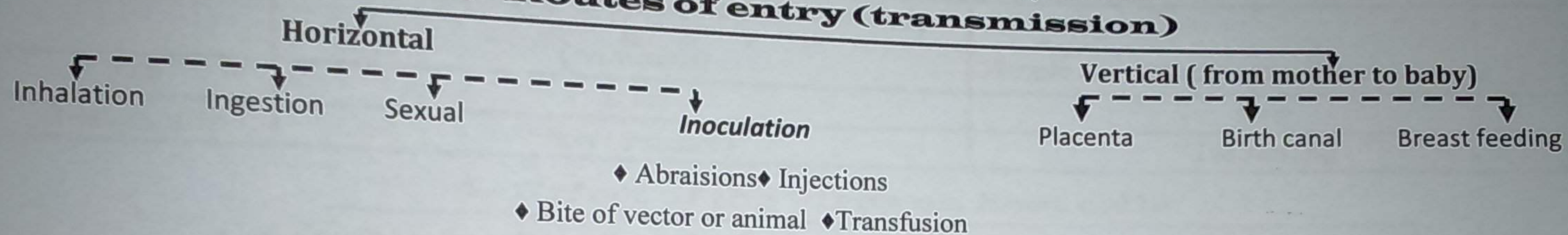




# Steps of viral pathogenesis

Is the interaction of virus & host factors → ds production

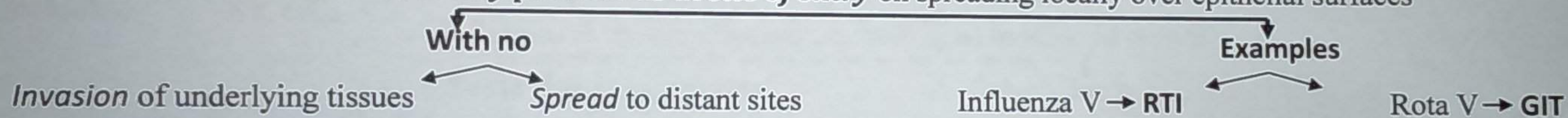
## 1 - Routes of entry (transmission)



## 2 - Local or 1ry replication

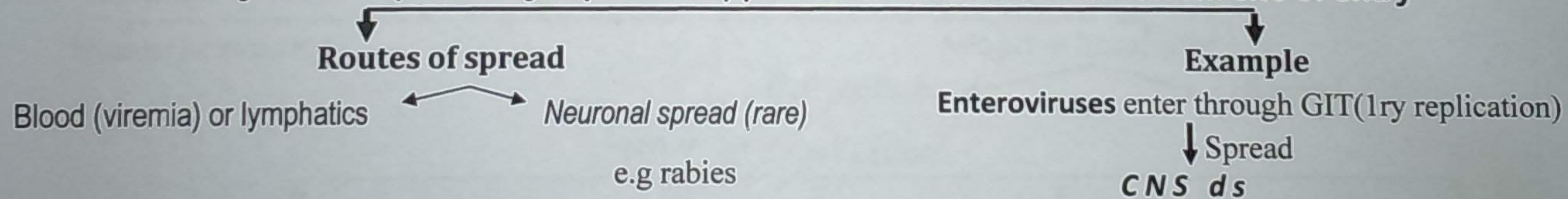
Viruses usually replicate at the 1ry site of entry

Some viruses *only produce ds at site of entry* on spreading locally over epithelial surfaces

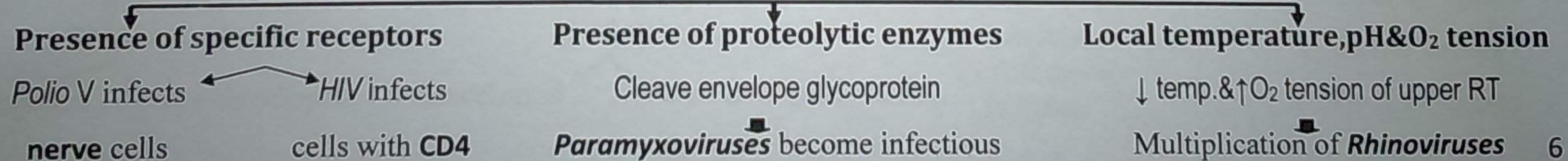


## 3 - Viral spread to target organs & cell tropism

a. Many viruses ( after 1ry replication ) produce ds at sites distant from site of entry



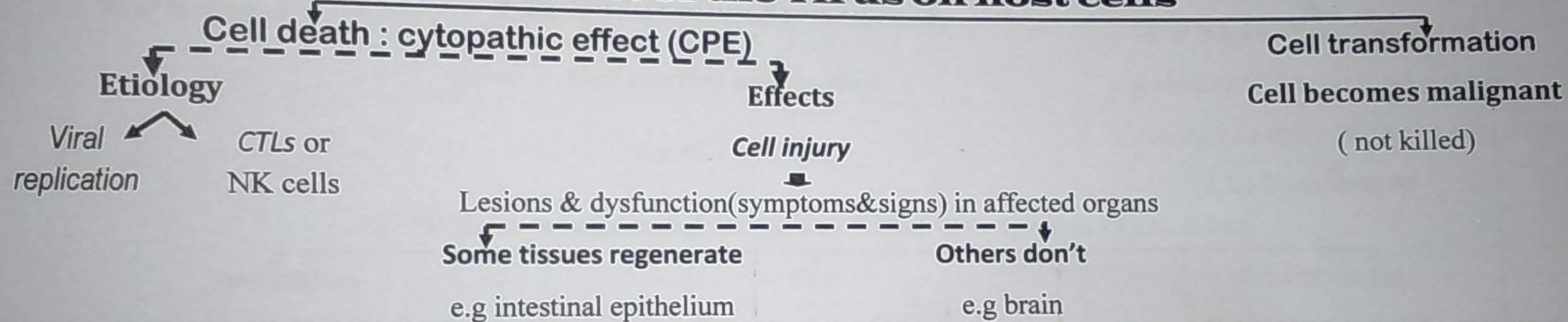
b. Mechanism of tropism (affinity to specific body tissues)



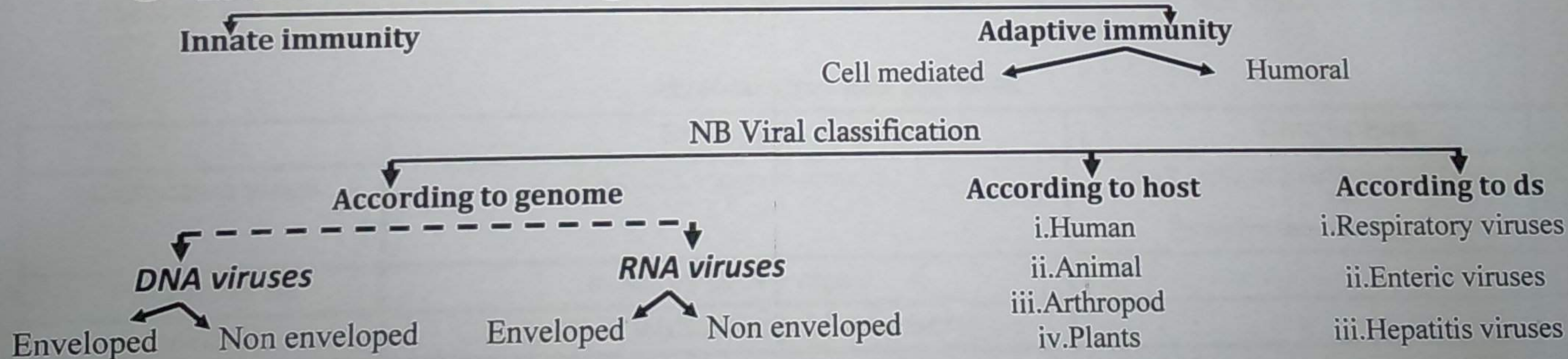


Types of viral diseases		
1-Characters	Localized ds	Systemic ds
	Viruses invade only tissues adjacent to site of entry (no viremia)	Viruses spread Viremia → invades many tissues & organs
2-IP	Short	Long
3-Immunity	Short (transient)	Long lasting

#### 4 - Effect of the virus on host cells



#### 5 - Host immune response & recovery from infection





## 6 - Fate of the virus after clinical recovery

Complete resolution

Viruses are completely eliminated from the body

↓

Viral clearance

Persistent viral infection

Chronic infection

V. persists in 1ry target

↓  
Slow replication

↓  
Mild or no symptoms & pt is infectious

↓  
Viral markers are detected

e.g HBV in liver

Latent infection

V. persists *away from 1ry target*

↓  
No replication ( *occult* )

↓  
No symptoms & pt isn't infectious

↓  
Viral markers *aren't detected*

e.g *Herpes V* in trigeminal ganglia

✓ Virus may be intermittently reactivated

↓  
Can be *recovered*

## 7-Virus shedding in the environment

Definition

The time at which the infected person become **infectious to contacts**

Site

From body surfaces involved in viral entry

No shedding

Occurs if *the human is dead – end host*

↓  
Not infectious e.g rabies

### Atypical virus like particles

	Structure	Characters
Defective virus	Viral NA + capsid protein	<i>Can't replicate without a helper virus</i> ↓ Provides the missing function
Pseudovirus	Host cell DNA + capsid	
Viroid	Circular RNA without capsid or envelope	
Prions	Infectious proteins with no nucleic acid	<i>Smallest infectious particle</i>



# Laboratory diagnosis of viral infections

## I-Direct demonstration of virus or its constituents in clinical specimens

### 1-Detection of viral particle by EM

For viruses of special morphology e.g Rota virus

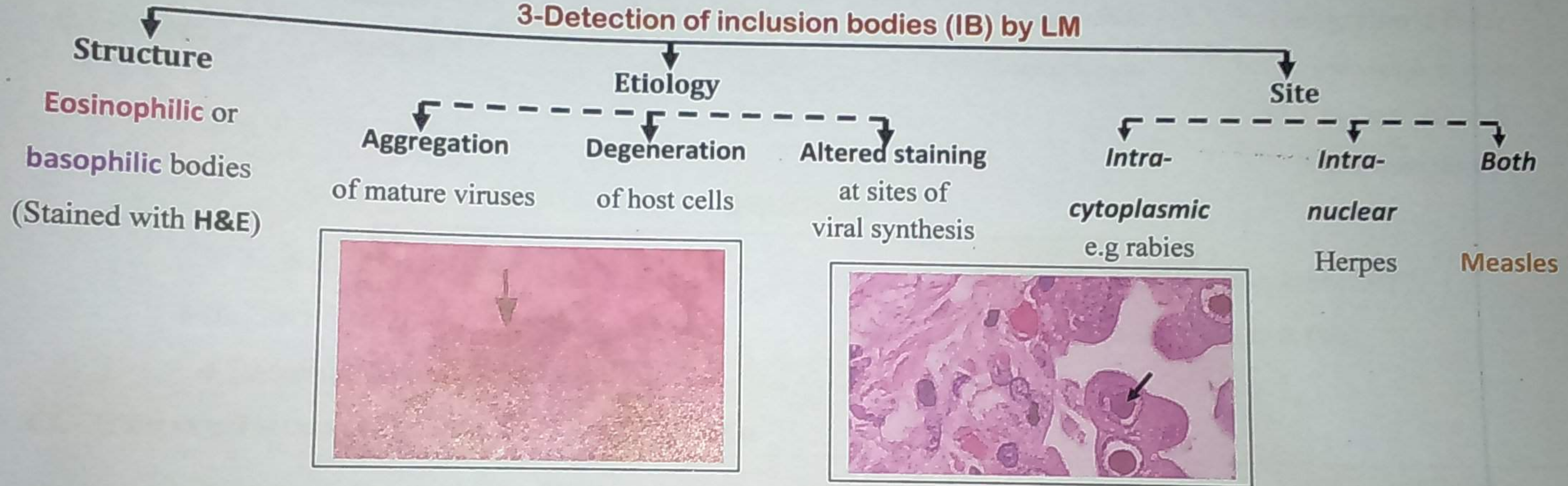
### 2-Detection of specific Ag (Addition of specific Abs)

ELISA

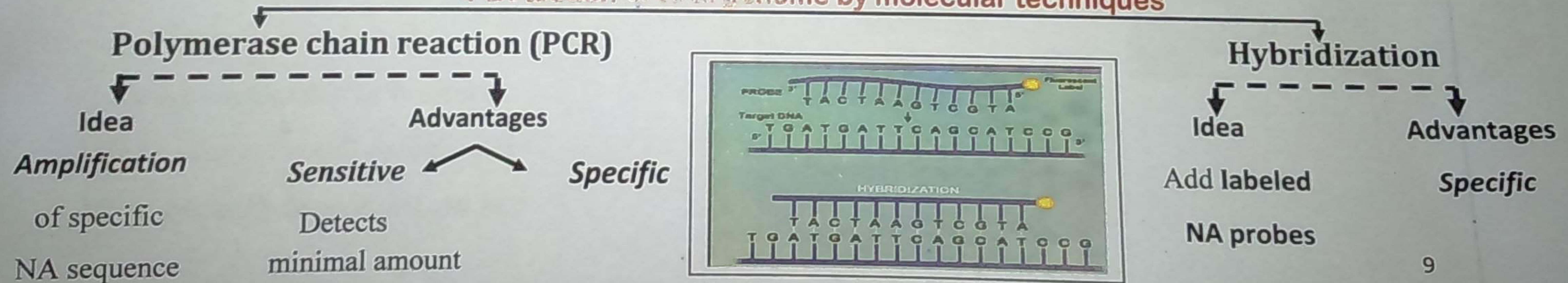
RIA

DIF

### 3-Detection of inclusion bodies (IB) by LM



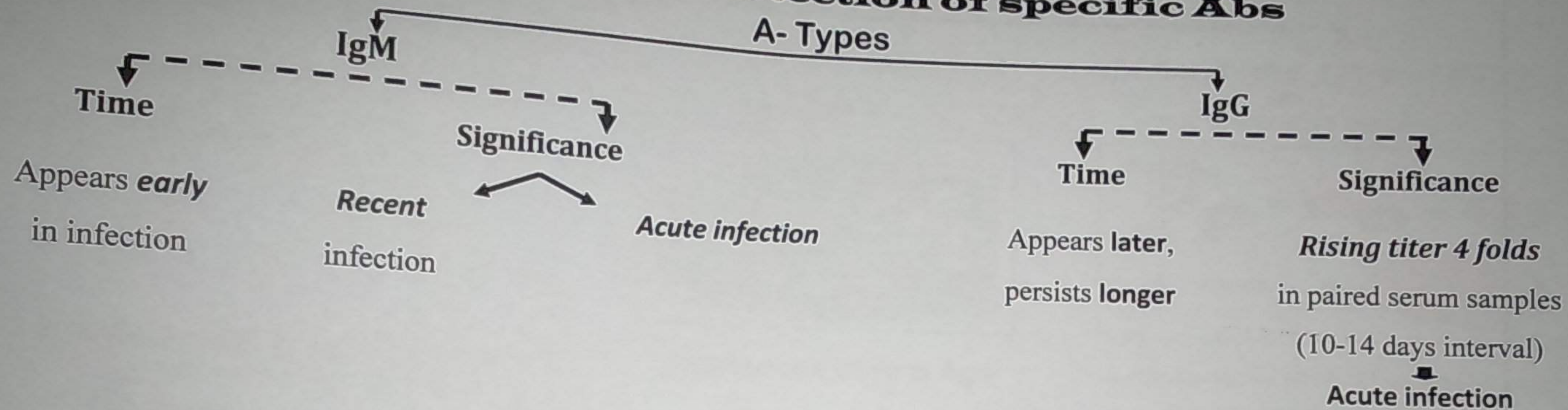
### 4-Detection of viral genome by molecular techniques





## II- Serological detection of specific Abs

### A- Types



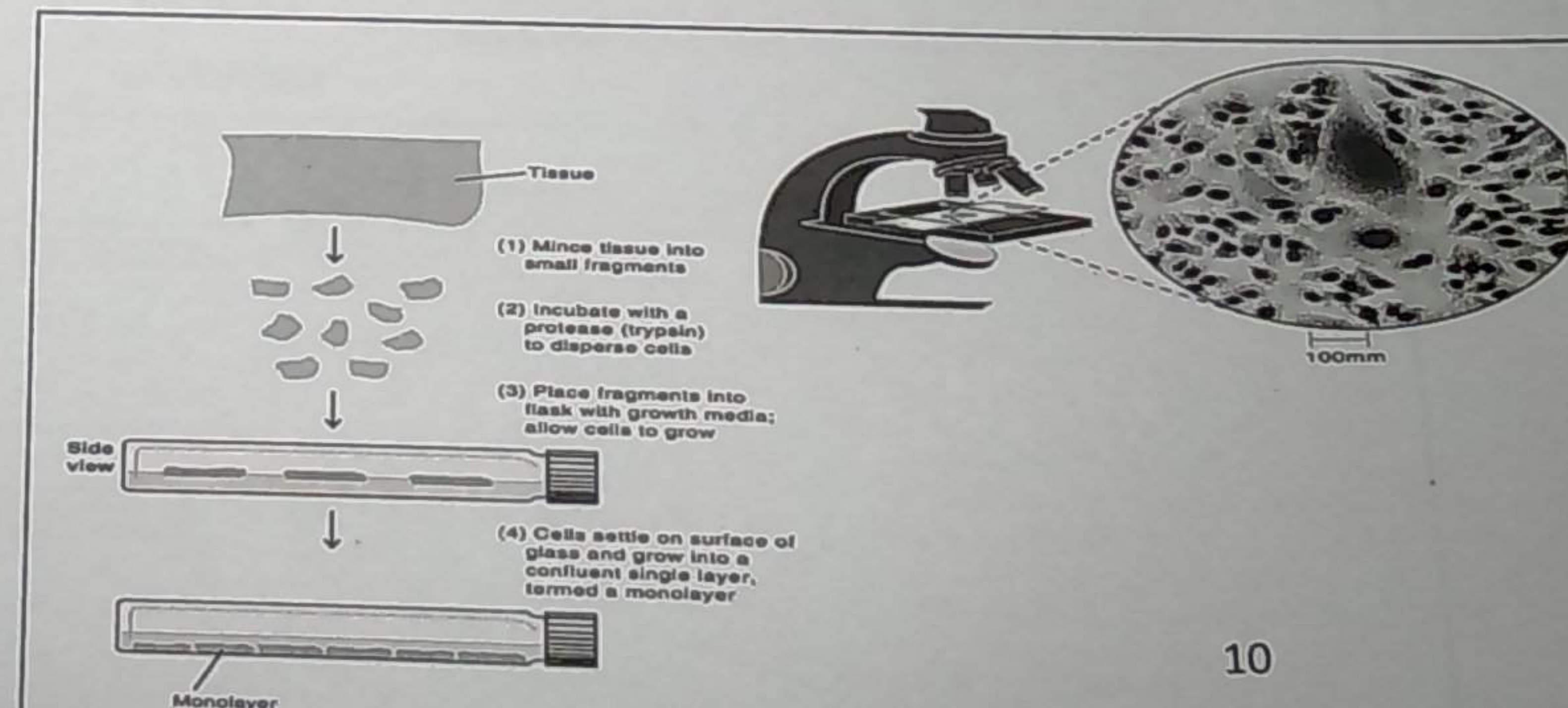
### B-Methods

- ♣ Indirect ELISA
- ♣ Indirect immunofluorescence
- ♣ Radioimmunoassay (RIA)
- ♥ Complement fixation test (CFT)
- ♥ Neutralization test (Nt)

## III-Virus isolation on living cells

### A-Tissue culture

Inoculation of virus on  
**living susceptible cell culture**  
 ↓  
 Virus infects the cell & replicates  
 ↓  
**Viral growth is recognized by:**





**Killing of cells**  
**Detachment**  
 from wall of TC flasks

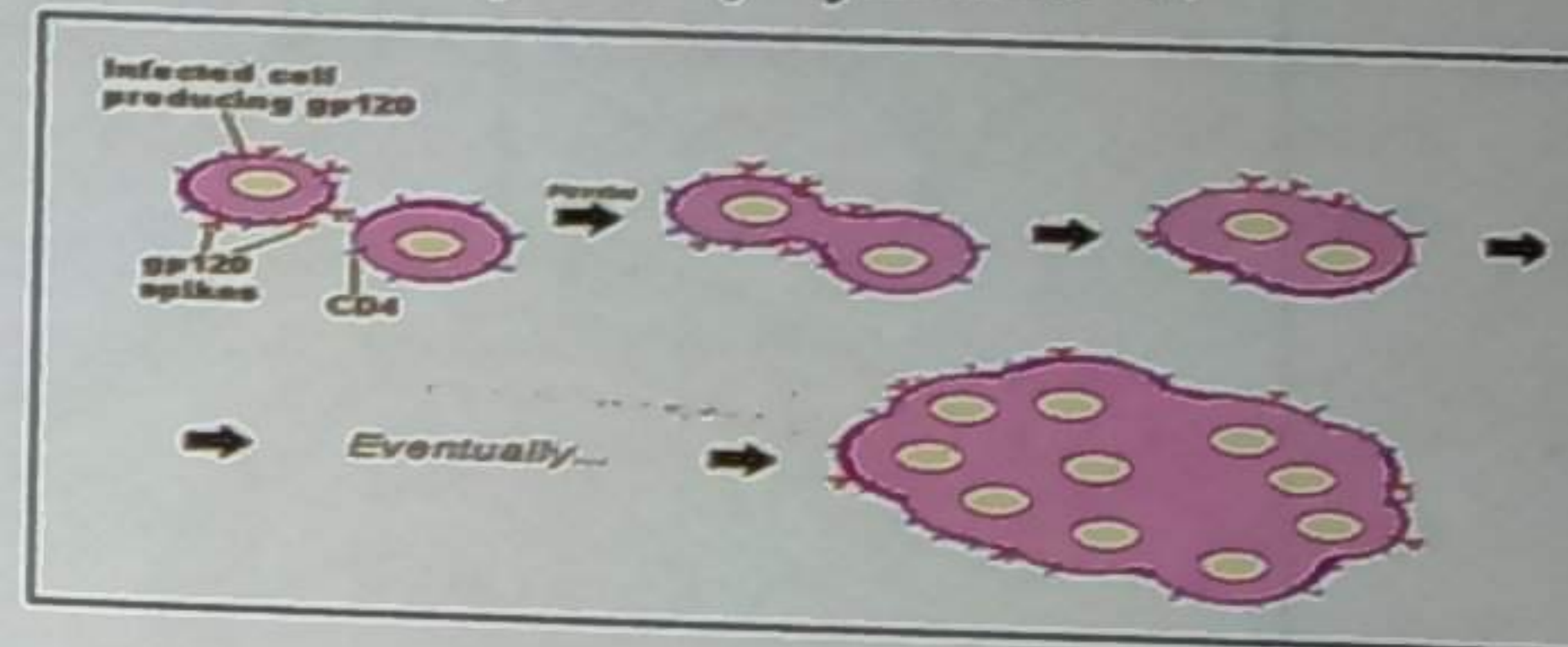
**Rounding of cells**  
 e.g Herpes V

## 1 - Cytopathic effect

**Grape - like cells**  
 e.g Adeno V



**Fusion of cells** **Syncytia (MGCs)**  
 e.g Respiratory syncytial V.



## 2-Inclusion body formation:by L/M

VICs stained  
 with H&E

e.g **Negri bodies**  
 in rabies V.

## 3-Detection of viral Ags

On surface of VICs  
 By DIF

## 4- Detection of viral Nucleic acid

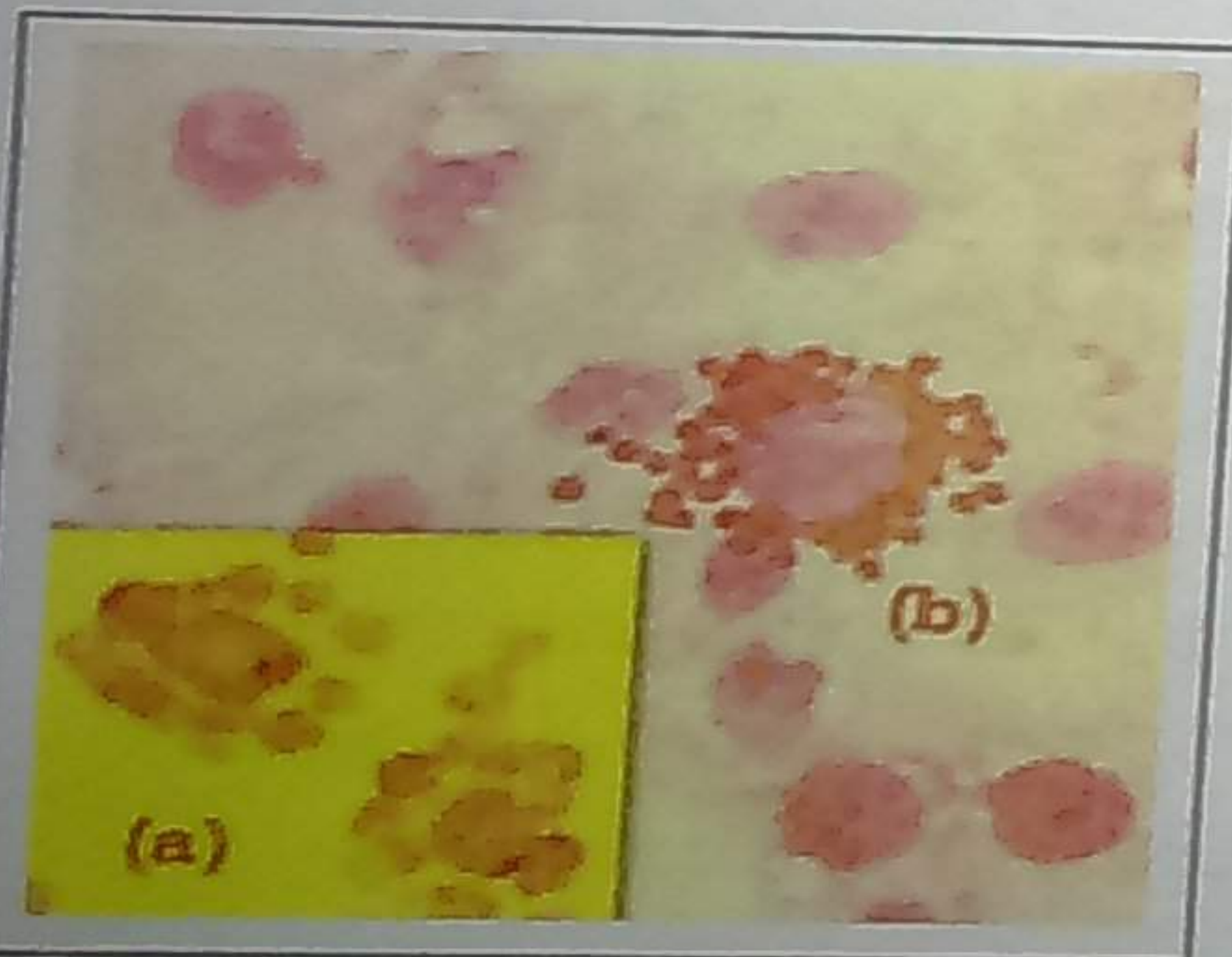
♦ PCR  
 ♦ Hybridization

♪ Rapid  
 ♪ Specific & sensitive

## 5-Hemadsorption

**Adsorption of RBCs on VICs**

Due to presence of viral hemagglutinin  
 e.g Influenza & Parainfluenza V

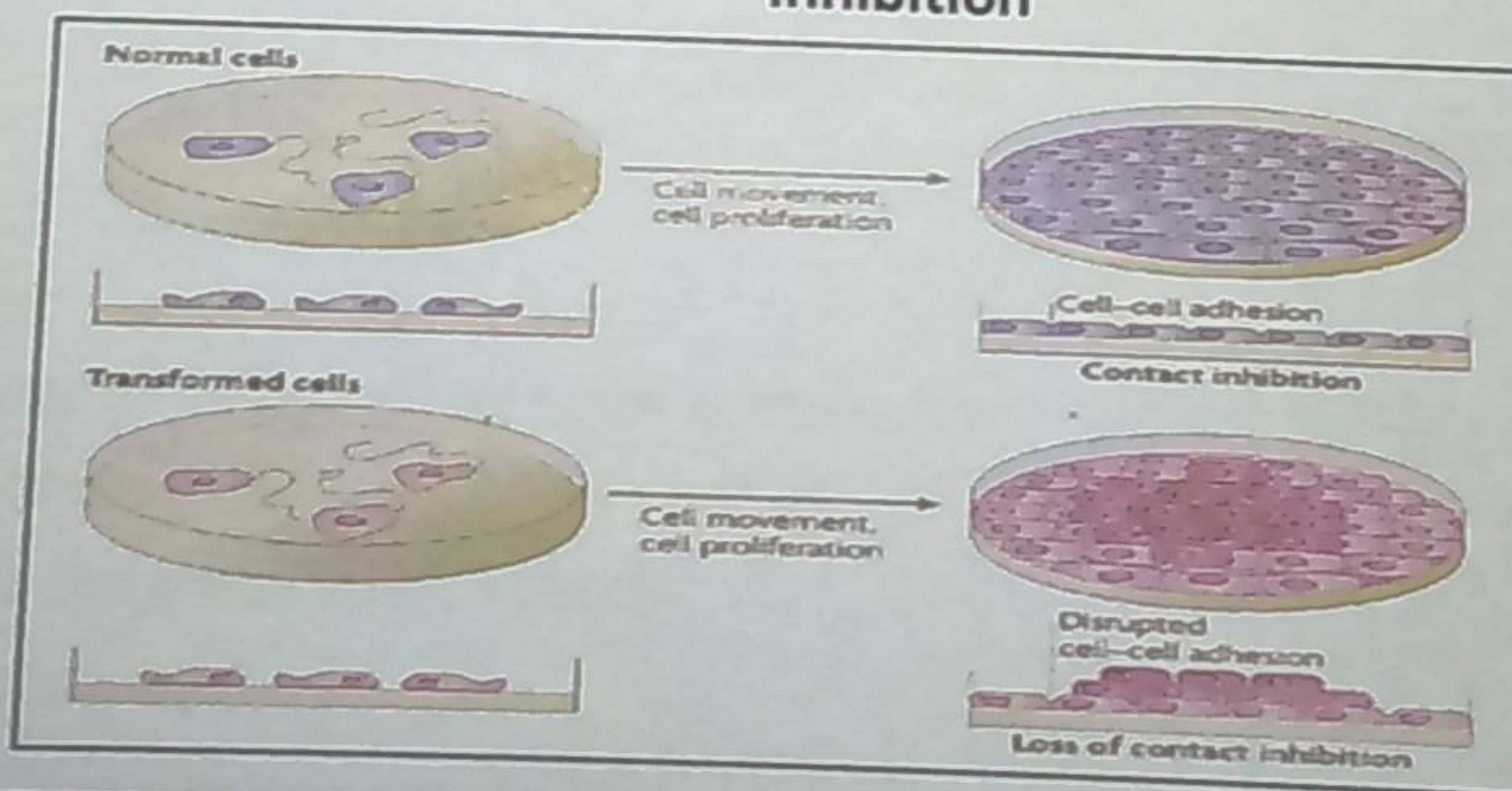


## 6-Transformation By oncogenic viruses

**Uncontrolled Growth**

**Loss of contact inhibition**

**Piling up of cells**



## 7-Interference

**Non cytopathic V. (e.g Rubella)**

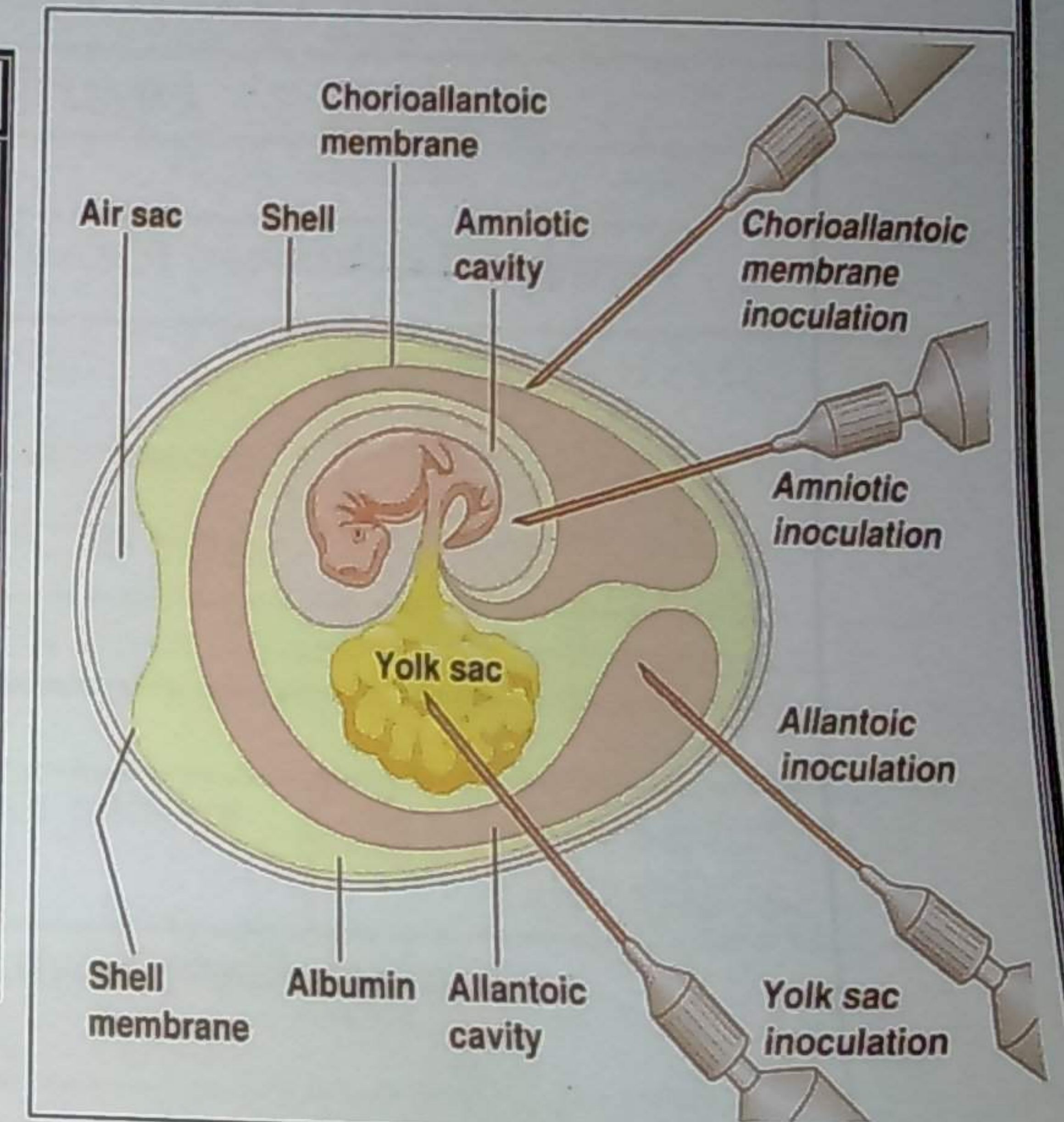
Interfere with replication & CPE produced by cytopathic V.

e.g Echoviruses  
 (added to TC as indicator)



## B - Laboratory animals & Chick embryo

	Laboratory animals	Chick embryo (rarely used)
1-Idea	Virus is inoculated <b>in laboratory animals</b> (e.g mice, rabbits or monkeys)	Virus is inoculated on <b>Yolk sac , amniotic sac or chorioallantoic membrane</b>
2-Identi- fication	<i>Ds or death of animal</i>	<i>i. Death of embryo ii. Production of hemagglutinin iii. Formation of pocks</i>
3-Uses		Mainly for viral multiplication ↓ <b>Production of vaccines</b>



### Essay Questions

1. Give an account on viral capsid.
2. Give an account on viral envelope
3. Give an account on eclipse phase of viral replication.
4. Give an account on inclusion bodies.
5. Give reasons : viruses exhibit tropism to different body tissue and cells
6. Compare and contrast between a systemic and a localized viral ds.
7. Compare & contrast between +ve & -ve sense RNA viruses regarding transcription & translation.





# Reaction of viruses to physical & chemical agents

Agents	Effect on viruses		
<b>A-Physical agents</b>			
<b>1-Heat</b>	Destroy all viruses at 60C for 30 min except hepatitis A&B viruses		
<b>2-Coldness</b>	i. Most viruses are stored at: - 40 or -70 (better)	<b>Lyophilization</b> Dryness+freezing under vacuum Preserve viruses at 4C for years	Some V are inactivated by <b>freezing</b>
<b>3-Radiation</b>	UV rays, X rays & γ rays (high energy particles) <b>affect NA</b> of viruses → inactivation		
<b>B-Chemical agent</b>			
<b>1-pH</b>	✓ Viruses are stable between 5&9	✓ Enteroviruses are resistant to acidity	☒ All viruses are <i>destroyed by alkalinity</i>
<b>2-Ether, alcohol &amp; other detergents</b>	Dissolve viral envelope → <i>inactivate enveloped viruses</i>		
<b>3-Oxidizing agents</b>	e.g Chlorine, iodine & H <sub>2</sub> O <sub>2</sub> → <i>Inactivate viruses</i>		
<b>4-Formaldehyde</b>	<b>Affect NA</b> without affecting viral Ags → Used to <i>prepare inactivated vaccine</i>		
<b>5- Salts e.g MgCl<sub>2</sub></b>	<b>Stabilize viruses in live attenuated vaccines</b> e.g Poliomyelitis vaccine Maintain potency for ws at high temperature in tropics		
<b>6- Glycerol (50%)</b>	<i>Preserve viruses, but destroy bacteria</i> → used to <b>decontaminate</b> viral preparations		
<b>7- Antibiotics</b>	No effect on viruses, but <b>kill bacteria</b>		
<b>8-Phenols</b>	Most viruses are <i>resistant</i>		



# **virology 2**

**DNA VIRUSES**

DNA VIRUSES



# DNA Viruses

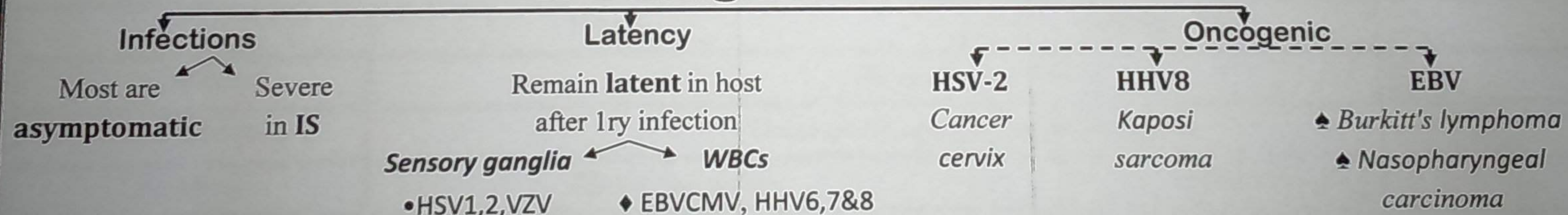
Enveloped		Non enveloped
Herpes family	Pox family	
1-Herpes simplex type 1&2 (HSV1&2) 2-Varicella-Zoster virus (VZV) 3-Human herpes type 6,7&8 (HHV 6,7&8) 4-Epstein-Barr (EBV) & Cytomegalo (CMV)	1-Small pox & Vaccinia 2-Molluscum contagiosum	1-Human papilloma (HPV) 2-Parvovirus B19 3-Adenoviruses 4-Polyoma viruses

## Skin & MM infections

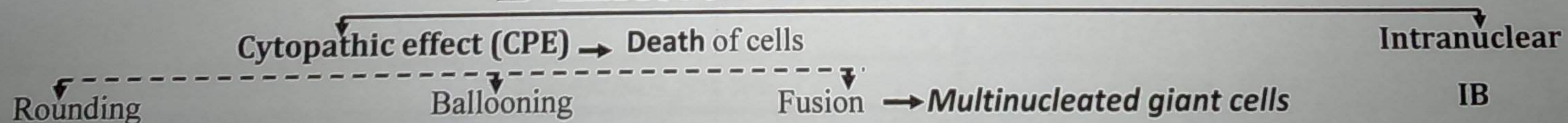
Herpes Simplex viruses		Varicella-Zoster virus		HHV 6&7	Pox viruses		Non enveloped V
HSV1	HSV2	Varicella	Zoster		Small pox	Molluscum	Human papilloma
♦Oropharyngeal	Genital (Oncogenic)	Generalized rash	Localized rash	Localized rash	Generalized rash	Skin wart&Genital lesions	
♦Skin :fingers						Benign	Oncogenic
	Neonatal	Neonat. & cong.					Neonatal
❖ CNS: encephal. ➤ Pneumonia	CNS:menig.	CNS:encephal. Pneumonia	CNS: CN				

## General characters of Herpes family

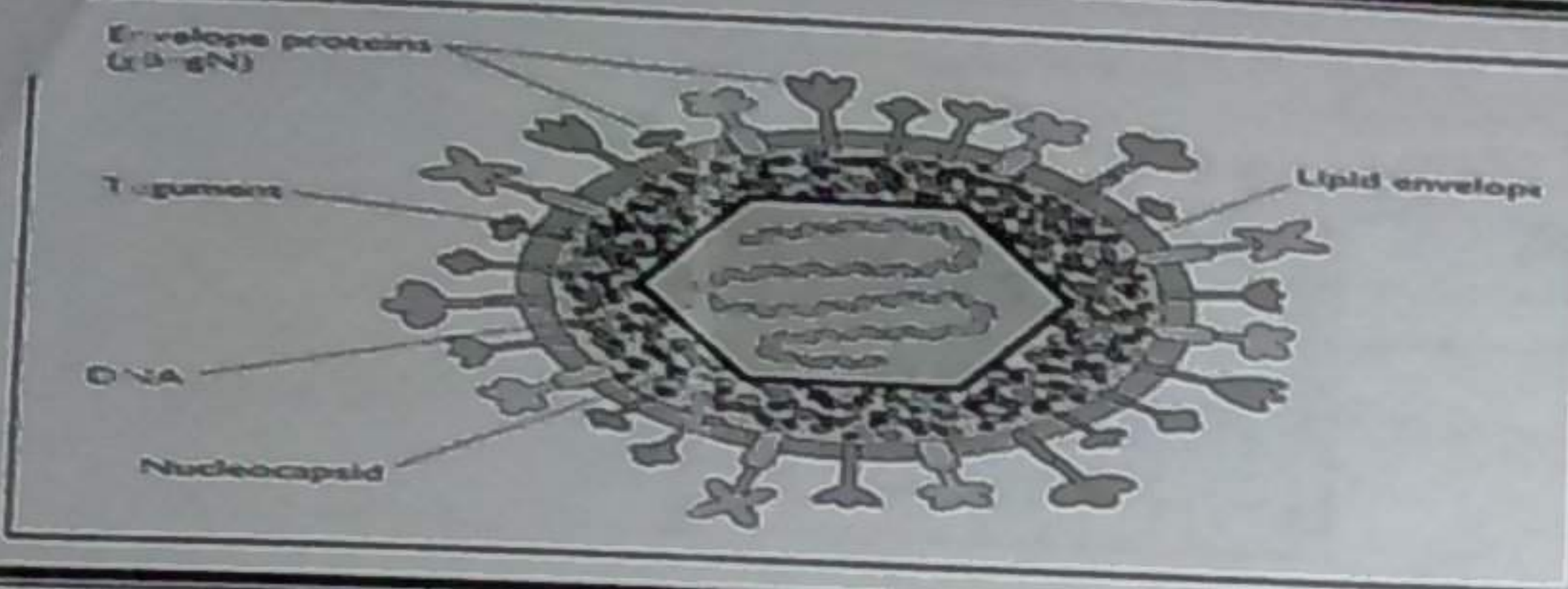
### A - Pathogenesis & disease



### B - Effect on Tissue culture







# Herpes simplex viruses type 1 & 2

## Common features between HSV1 & 2

	HSV 1	HSV2
1-Same structure	<b>i-Genome :</b> Ds DNA <b>ii.Capsid :</b> Icosahedral <b>iii.Enveloped</b>	
2-Reactivations are common by :	<b>i.Physical</b> <b>ii.Physiological</b> <b>iii.Pathological</b> ♦ Sunlight      ♠ Stress ( long exposure)      ♠ Menstruation ♠ Pregnancy      ♣ High fever ♣ Common cold	
3-Pathogenesis : 1ry infection & Latency	Virus replicates in the <b>skin or MM</b> at the site of infection ↓ Migrates <b>up the neuron</b> → <b>latency in sensory ganglia</b>	
4-Immunity	Abs don't prevent reactivation as viruses are <b>hidden in neurons</b>	

## Differences between HSV1 & 2

	HSV1	HSV2
1-Genome	RE analysis of DNA	
2-Type specific Ag	Detected by specific <b>monoclonal Ab</b>	
3-Lesions	<b>Above</b> the waist	<b>Below</b> the waist
4-Modes of transmission	<b>Contact</b> with infected vesicle or saliva	☺ <b>Sexual</b> ☺ From <b>infected maternal genitalia</b> to newborn
5-Latency	<b>Trigeminal ganglia</b>	<b>Lumbar or sacral ganglia</b>



# Diseases caused by HSV1

## A - Recurring lesions



### 1-Oropharyngeal lesions

#### i.Acute gingivostomatitis

\* 1<sup>st</sup> infection in *childhood*

By kissing from older person

\* **Generalized** : painful vesicles in oral cavity

↓  
Ulcer → Spontaneous healing in 2 wks



#### ii.Herpes labialis

(fever or cold sores)

Recurrent

form

Milder

Localised vesicle

in lips or nose



### 2-Herpetic keratoconjunctivitis

#### i.1<sup>st</sup> infection

Ulcers in cornea

&

eye lids



#### ii.Recurrence

Dendritic ulcer

↓  
Corneal scarring &

opacity

↓  
Blindness



## B - Other lesions

### 1-Skin ds

#### i.Herpetic whitlow

Fingers contact with infected vesicles

✓ Dentists

✓ Nurses

✓ Thumb-sucking

children



#### ii.Eczema herpeticum

Vesicles on  
eczematous  
children



### 2-CNS infections

#### Encephalitis

in **temporal lobe**

↓  
Fatal



### 3-Disseminated infection

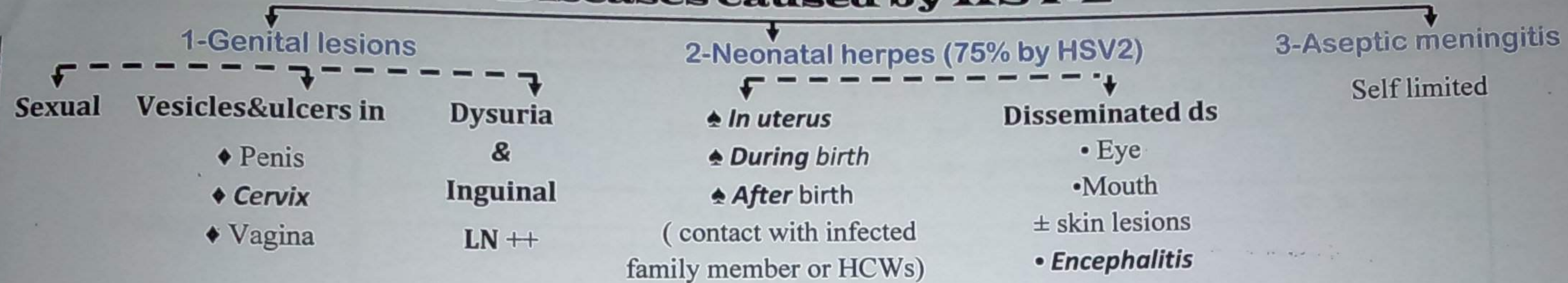
#### Pneumonia

in IS pts

in IS pts



## Diseases caused by HSV-2



Mother with active herpes infection (although active infection may not be apparent)



## Varicella Zoster virus (VZV)







Varicella (Chicken pox )		Zoster (Shingles )	
1ry inf. in childhood	Generalized	Reactivation	Localized

### Congenital & Neonatal Varicella

	Congenital Varicella	Neonatal Varicella
1-Acquisition	During 1ry maternal infection, virus crosses placenta in 1 <sup>st</sup> trimester	i. Last week of pregnancy. ii. Just after birth
2-Lesions	Fetal malformations	Disseminated Varicella



## Comparison between Chicken pox & Small pox

Comparison between Chicken pox & Small pox		
	Chicken pox :Herpes family	Small pox :Pox family
1-Pathogenesis	i.Virus infects mucosa in upper RT → Local LNs 1ry transient viremia → inf.of RES : liver & spleen 2ry viremia → <b>generalized rash</b>	
	ii.Latency In <b>dorsal root</b> or <b>trigeminal</b> ganglia ( nerve) ↓ Reactivation → <b>Zoster</b>	ii.No latency
2-Mode of transm.		
a.Droplet	From case of Varicella	From case of small pox
b.Contact with vesicles	From case of Varicella or Zoster	
3-Clinical picture	Mild fever	
Rash	Stages : macule→ papule → vesicle → pustule →crust	
i.Distribution	<b>Centrifugal</b> 1 <sup>st</sup> on trunk ↓ face & limbs 	<b>Centripetal :</b> 1 <sup>st</sup> on face, arms & legs ↓ hands & feet 
ii.Stages	<b>Cropping :</b> all stages are detected simultaneously 	<b>No cropping</b> 
iii.Fate	Crust → healing → <b>no scar</b> ✓ The ds is more <b>severe</b> in <b>adults</b>	Crust falls → <b>permanent scar</b> (Pt is contagious until crusts fall off)
<div><div><p>ASPIRIN</p></div><div><p>Complications of Chicken pox( most pts recover rapidly )</p><p>i.Pneumonia &amp;keratitis in IS or adults pts</p><p>ii.Reye's syndrome (rare)</p><p>Encephalitis &amp; hepatic ds following <b>salicylate</b> intake</p></div><div><p>Fatty Liver Disease</p></div></div>		

5





## Zoster (Shingles)

A-Etiology (sporadic)

*Reactivation of latent VZV in*

Adults  $\longleftrightarrow$  IS pts

B-Clinical picture

Severe pain

↓ Few days

Rash similar to Varicella but

*Unilateral*

Limited to skin innervated by *dorsal root ganglion*

C-Complications

**Eye via trigeminal nerve: HZ ophthalmicus**

Conjunctivitis



Keratitis



Iritis

**Post herpetic neuralgia**

Severe debilitating pain

in affected areas even  
after clearance of rash

Duration

- Few ws or ms usually
- Many yrs rarely

**Rare complications**

- \*Blindness
- \*Hearing loss
- \*Pneumonia
- \*Encephalitis
- \*Death

**Causes of eradication of small pox (since 1980)**

Control of transmission

Efficient IR

Diseased individuals  
are the **only source**

No animal reservoir  
or carrier

Easy  
diagnosis

Single stable serotype  
↓  
Long lasting immunity

Efficient  
live vaccine

**Small pox is notable in medicine history**

1<sup>st</sup> vaccine : *Live attenuated vaccinia virus*

Given to children by scarification

1<sup>st</sup> eradicated ds


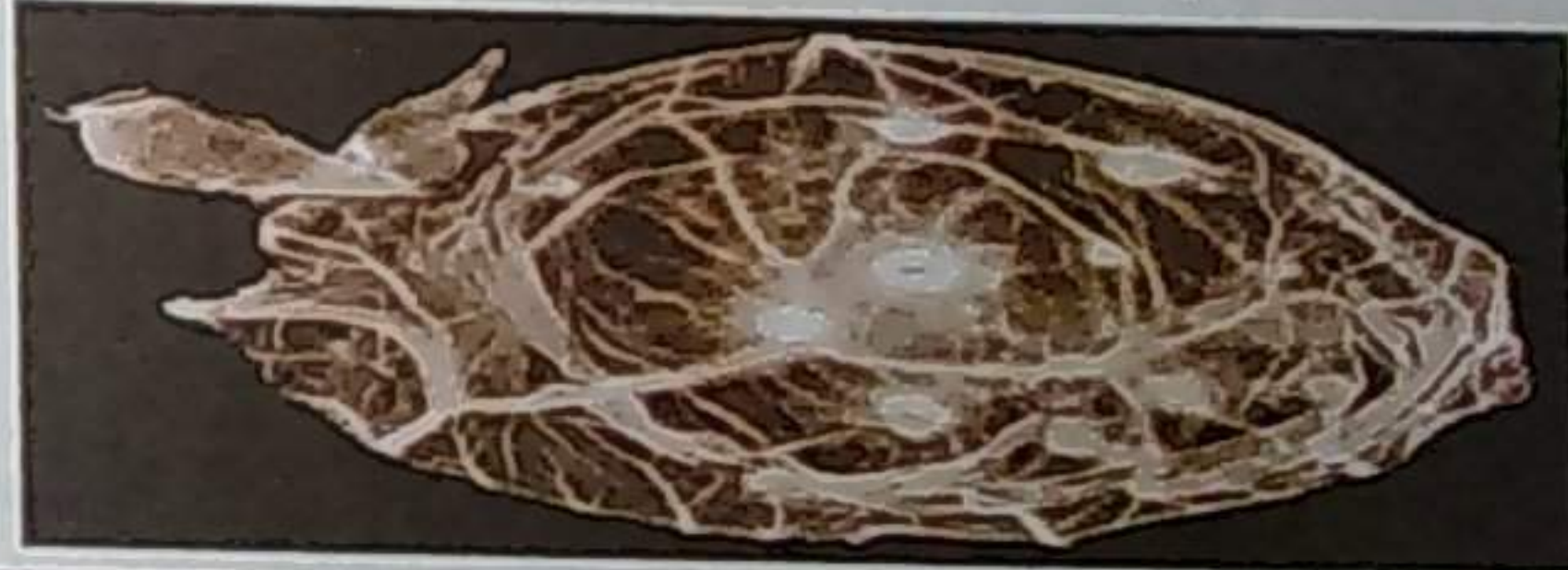
Potential use as **biological weapon**







Treatment		
	HSV 1 & 2	VZV
1-M. of action	Acyclovir	
2-Selectivity	⊖ viral DNA polymerase → Doesn't affect virus in latent stage	
3-Indications	Affect only VIC as viral thymidine kinase activates the drug	
	i. Eye & skin lesions : topical ii. Reactivation of latency in IS pts : IV	i. IS children    ii. Zoster pts ii. Complicated Varicella : Pneumonia & keratitis iii. Neonatal Varicella

Prevention			
	HSV 1 & 2	Varicella (Chicken pox)	Zoster
1-General	1 - Avoid contacts with skin lesions		
	2-Cesarian section : For pregnant ♀ with genital herpes Prevent neonatal herpes		
2-Chemoprophyl.	Acyclovir : For IS pts e.g transplant recipients Prevent reactivation		
3-Vaccine			
a. Type		Live attenuated SC (Zoster Vac.contains 14 times more virus than Varicella Vac.)	
b. Administration		2doses for children between 1-12 yrs	1dose ≥ 60 yrs
c. Contraindications		i. Immunocompromised people	ii. Pregnant ♀
4-Passive		Specific VZ Igs 1. IS children:exposed to inf. 2. Infected pregnant ♀: i. Before delivery ii. Their newborns; immediately after delivery	



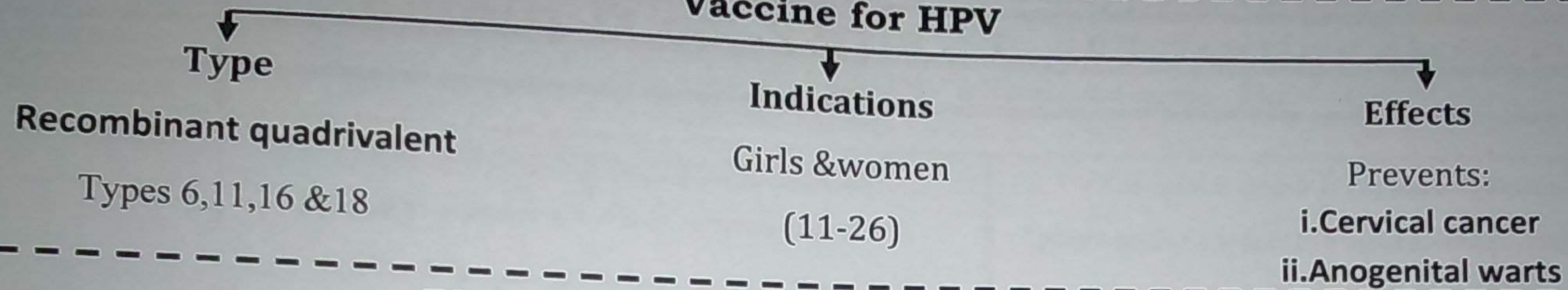
Laboratory diagnosis			
I-Specimen	HSV	VZV	Small pox
	1 - Vesicular fluid		
II-Direct virus demonst.	2-Scrapping from ulcer or cornea		
A-EM	Detects viral particles		
B-LM (Rapid & diagnostic)	<i>i. Multinucleated giant cells</i> : Using <b>Tzank smear</b> Cells from vesicles stained with Giemsa 		Detects viral particle
	<i>ii. Intranuclear IB : Cowdry bodies</i>		
C-DIF	Detects viral Ag		
D-PCR	Detects <b>DNA in CSF</b>	Detects DNA in vesicles	
III-Virus isolation	<i>On tissue culture :</i> <b>CPE &amp; Intranuclear IB</b>		<i>On chick embryo (most reliable) in chorioallantoic membrane:</i> <b>Intracytoplasmic IB + pocks</b> 
IV-Serology : ELISA	1-Ig <b>M</b> : <b>1ry</b> (current) infection 2-Ig <b>G</b> : <b>past</b> infection (Recurrence isn't associated with ↑ IgG)		<b>Specific Ab</b> Confirm diagnosis



Human papilloma virus		Molluscum contagiosum V.
1-Structure		
a.Genome & Capsid	D s D N A & I c o s a h e d r a l	
b.Envelope	Non enveloped	
c.Types	> 60 types according to DNA homology	Enveloped
2-Modes of trans.	i.Cutaneous lesions : direct contact or through fomites      ii.Genital lesions : sexual transmission	
3-Pathogenesis	Epithelial proliferation	
	i.Cutaneous → self limited	ii.Genital → oncogenic
		Non oncogenic
4-Disease	<p><b>a.Cutaneous infections</b> : common warts</p> <p>♠ Hands      ♠ Soles (plantar warts )</p>  <p><b>b.Mucosal infections</b></p> <p><i>i.Condyloma accuminata (type 6&amp;11)</i> Malignant in IS pts <u>Invasive squamous epithelioma</u></p>  <p><i>ii.Juvenile laryngeal papilloma</i> From mother <u>birth canal</u> infected with <u>genital warts</u></p>  <p><i>iii.Cancer cervix : type 16 &amp; 18</i></p>	
	<p>Benign <b>wart-like</b> lesions on face, arms &amp; genitalia</p> <p><b>Spontaneous healing</b> in 2-6 ws</p> <p><b>No malignancy</b></p>  <p>✓ NB.virus is <b>weak Ag</b></p> <p><b>No serological tests</b></p>	
5- Laboratory diagnosis	<p>Direct demonstration of virus in specimen</p> <p>i- PCR : detects viral DNA</p> <p>ii-Hybridization</p> <p>ii.EM : detects viral particle</p>	
6-Treatment	NO antiviral drugs	

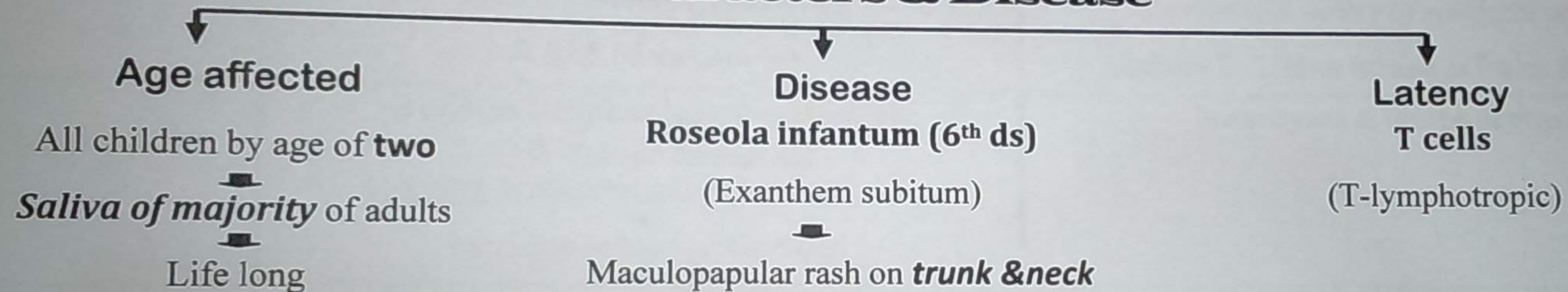


### Vaccine for HPV



### Human Herpes Viruses 6 & 7


#### Characters & Disease



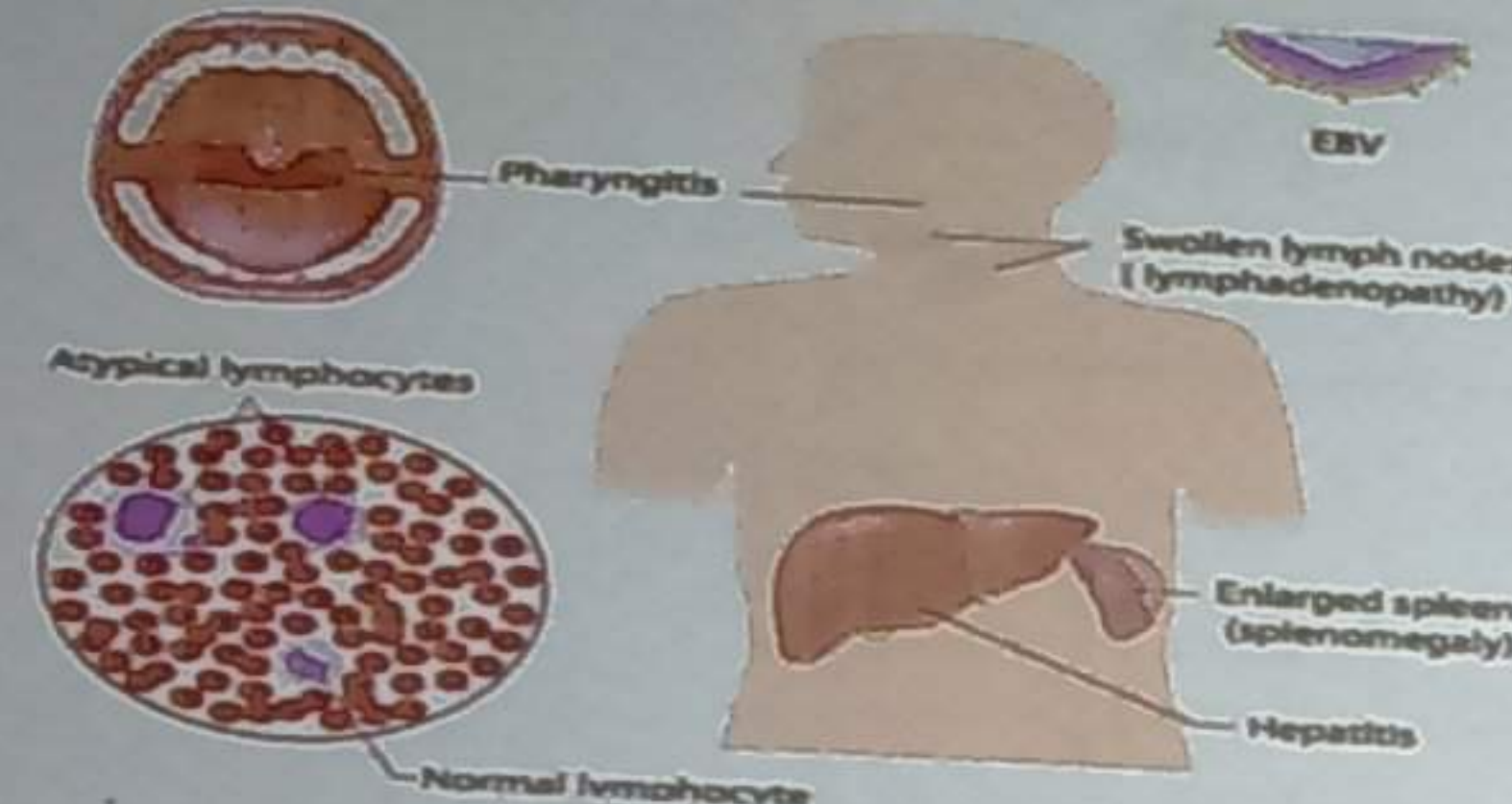

### RES & BLOOD infections

Epstein Barr Virus (EBV)	Cytomegalovirus (CMV)	Parvovirus B19
Infectious mononucleosis		Anemia
Congenital infections		
Oncogenic		Skin rash :localized



	Epstein Barr Virus		Cytomegalovirus
I - Structure	i. Ds DNA ii. Icosahedral capsid iii. Enveloped		
II - Pathogenesis			
A-Acute infection	<p>Virus infects <u>nasopharyngeal epithelium</u></p> <p>↓</p> <p>Spread to <b>salivary glands</b> &amp; oropharyngeal L.T</p> <p>↓</p> <p><b>Infects B lymphocytes that spread the virus</b></p> <p>↓</p> <p><u>Viremia</u></p> <p>↓</p> <p>Infection of more lymphocytes &amp; RES (liver &amp; spleen)</p>		<p>Virus infects upper RT &amp; <b>local lymphocytes</b></p> <p>↓</p> <p><b>Lymphocytes spread the virus</b> to other lymphocytes &amp; monocytes in spleen and LNs</p> <p>↓</p> <p><u>Viremia</u></p> <p>↓</p> <p>Spread to a variety of epithelial cells</p> <p><b>i. Salivary G ii. Kidney tubules iii. Testes &amp; ovary</b></p>
B-Latent infection	<p><b>*B cells &amp; Oropharyngeal epithelium</b></p> <p>❖ <b>Tumor formation</b></p> <p><u>Integrates</u> in host chromosome (sometimes)</p> <p>↓</p> <p>Indefinite cellular proliferation</p>		<p><b>Monocytes &amp; lymphocytes</b></p>
C- IR	<p>1-Elicits both <b>CMI (main) &amp; HI</b> → maintain virus in a <b>latent state</b> → <b>Reactivation in IS</b></p> <p><b>2-Atypical T lymphocytes</b></p> <p>CTLs destroying virally infected B cells → ↓ their n</p>		
III - Modes of Transmission	<p><b>Intimate contact with infected saliva (main)</b></p> <p><u>Kissing ds</u></p> <p><b>NO KISSING!</b></p> 		<p><b>1-Close contact with body secretions as saliva, urine, vaginal secretions &amp; semen</b></p> <p><b>2-Blood transfusion &amp; transplacental</b></p> <p><b>3-Organ transplantation (liver &amp; Kidney)</b></p> <p><b>4-Sexual intercourse</b></p> <p><b>5-Perinatally :</b></p> <p>i. Passage in infected birth canal ii. Breast feeding</p>



III-Diseases	EBV		CMV
<b>A-Normal host</b> 	<b>EBV</b> <b>1-Asymptomatic in older children &amp; adults</b> Affects <b>95%</b> of normal population <b>2-Infectious mononucleosis syndrome (self limited)</b> i. Fever & pharyngitis ii. Lymphadenopathy iii. Hepatosplenomegaly, <b>hepatitis</b> ± jaundice <b>iv. +ve heterophil Abs</b> : Abs agglutinate <b>Sheep RBCs</b>		<b>CMV</b> Flu-like symptoms
<b>B-Immuno-compromised host</b>	<b>iv. +ve heterophil Abs</b> : Abs agglutinate <b>Sheep RBCs</b> ♦ Transplanted pts   ♦ AIDS pts   ♦ Pts receiving IS drugs <b>More severe ds</b> 		iv. -ve heterophil Abs <b>1-Pneumonia</b> 2-Rejection of renal & liver allografts <b>3-Retinitis → blindness</b> 4-Encephalitis, colitis & oesophagitis
<b>C-Other diseases</b>	<b>Malignancies: 1-Burkitt's lymphoma 2-Nasopharyngeal carcinoma</b>		<b>Congenital &amp; neonatal infections</b>

**A - Congenital infections of CMV**

**1-Modes of transmission : in uterus**

With both **1ry & reactivated** maternal inf.      At any stage of pregnancy

**2-Effects**

**Abortion  
or Stillbirth**



• Brain calcification • Microcephaly • Mental retardation

**CNS**

**Cytomegalic inclusion disease (CID)**

**Retinitis &  
Ocular defects**

**Deafness**

**Hepatomegaly &  
Jaundice**



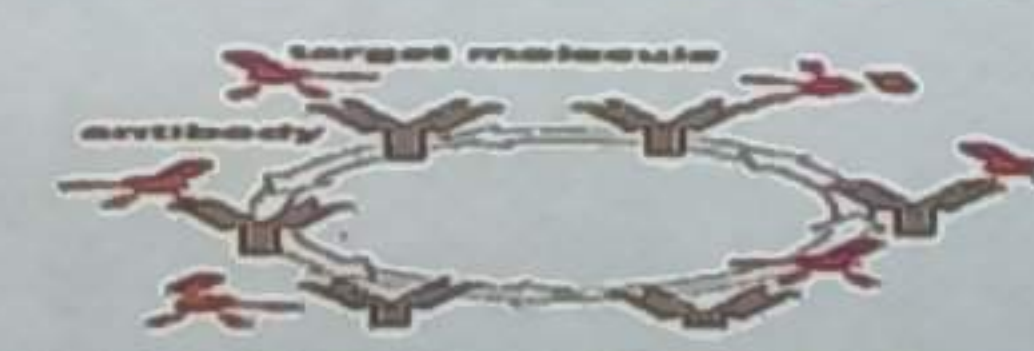
**B - Perinatal infections**

**1-Modes of transmission : a. From birth canal   b. Breast milk**

**2-Effects**

**Asymptomatic (usually)**

Infected neonates have **high titers of maternal Abs(IgG)**



**Hepatitis & pneumonia (uncommon)**





# Parvovirus B 19

## Structure

Small

SS RNA +ve sense or -ve sense

Icosahedral

Non enveloped

## Modes of transmission

Droplet

Blood transfusion & blood products

Transplacental



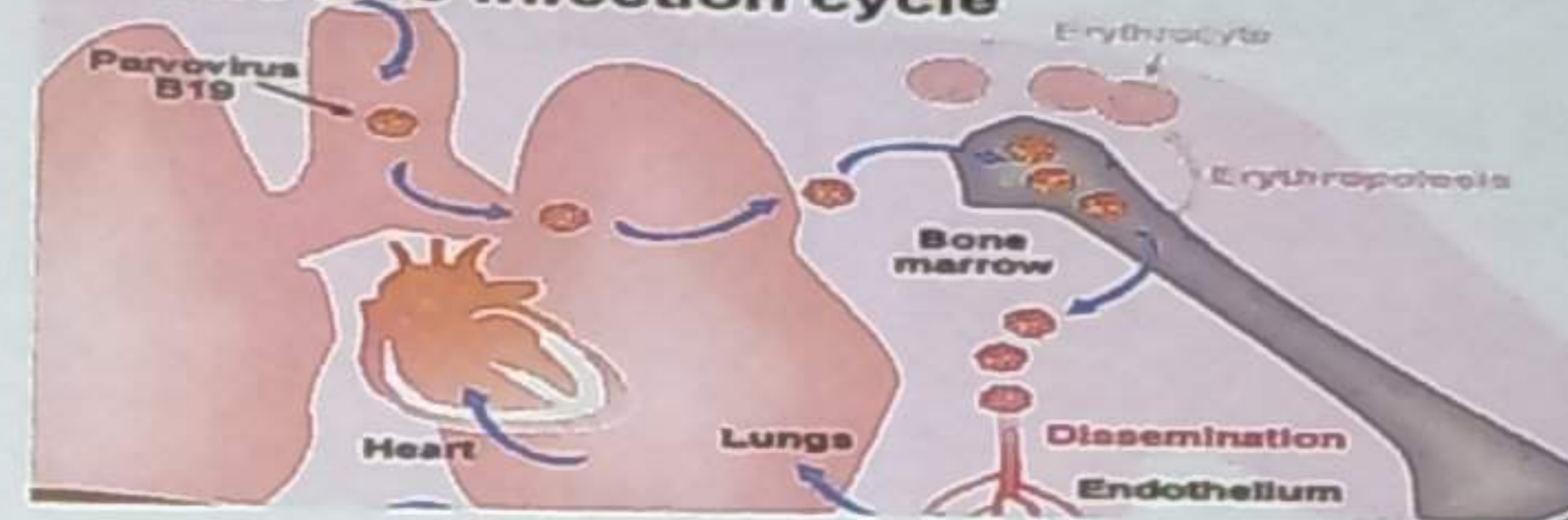
## Pathogenesis

### Target & Replication

**Immature RBCs** in adult BM & fetal liver

Interruption of RBCs production

### Parvovirus B19 Infection cycle



### Immunity & Persistence

Ab neutralize the virus

Persistence of infection

in *immunocompromized* pts

## Disease production



**1-Erythema infectiosum (5<sup>th</sup> ds)** : most common

IC deposition

**Slapped cheek rash**

in children

**Arthritis**

in adults



## 2-Anemias

### Transient aplastic crisis (TAC)

**Temporary** arrest  
of RBCs  
production

Apparent only in pts  
with **chronic**  
**hemolytic anemia**

**TAC**

### Pure red cell aplasia (PRCA)

**Persistent inf.**  
**Severe chronic**  
**anemia**

In IC  
pts

**PRCA**



### Non immune Hydrops (erythroblastosis) fetalis

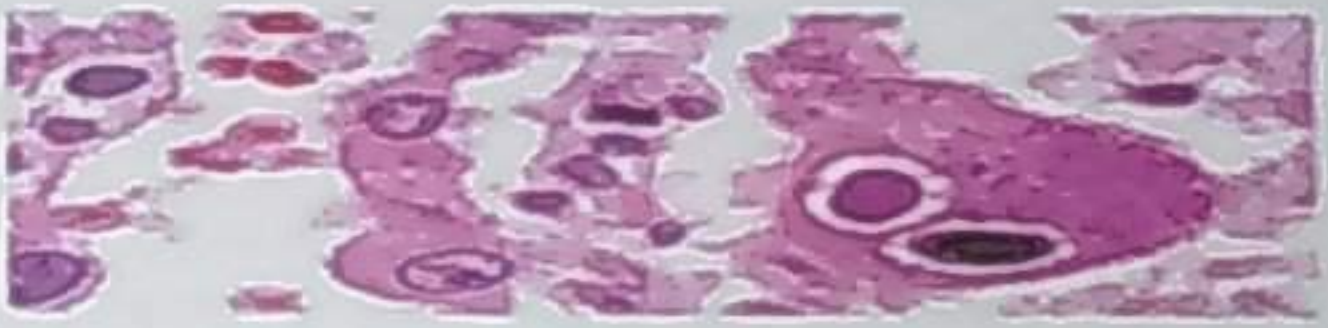



**Congenital inf.**

from 10<sup>th</sup> to 20<sup>th</sup> w of pregnancy



**Arrest** of fetal RBCs production

**Severe anemia**



Laboratory diagnosis			
I-Specimen	EBV	CMV	Parvovirus B19
	1-Peripheral blood mononuclear cells 2-Saliva		1-Blood cells 2-Respiratory secretions
	3-Lymphoid tissue	3-Urine	3-Tissue samples
II-Direct detection			
A-PCR	Detection of viral DNA → most sensitive method → routine detection		
B-Detection of Ag			
C-LM			
		DIF & ELISA 1-Multinucleated <i>giant</i> cells 2-Intranuclear owl's eye IB 	
III-Serology			
A-Specific Abs:ELISA	Anti VCA (viral capsid Ag)		
1-IgM	Recent infection		
2-IgG	Persists for life → indicates <i>past infection &amp; potential for reactivation</i>		
  	<b>B-Non specific heterophil Abs</b> By <i>Paul Bunnell &amp; monospot tests</i> Transient Abs in acute infection Agglutinate sheep RBCs		
	IV-Blood picture		
	1-Absolute <i>lymphocytosis</i> 2- <i>Atypical T lymphocytes</i>		



Treatment	
CMV	Parvovirus B19
In IS pts	In IS pts (PRCA)
Gancyclovir	1-Blood transfusion
	2-Ig preparation
	Neutralize viruses  Cure persistent inf.

Prevention	
CMV	Parvovirus B19
1-Screening	
of transplant donors & recipients for CMV Abs	of blood donors
2-Good hygienic practices e.g careful hand washing	
After contact with diapers or oral secretions	Prevent spread through respiratory secretions & fomites
3-Isolation of newborn with CID from other newborns	3-Standard inf.control precautions Protection of HCWs from pts with TAC or chronic PRCA

No antiviral treatment or specific prevention for EBV

## Other infections

Adenoviruses	HHV 8	Polyoma viruses
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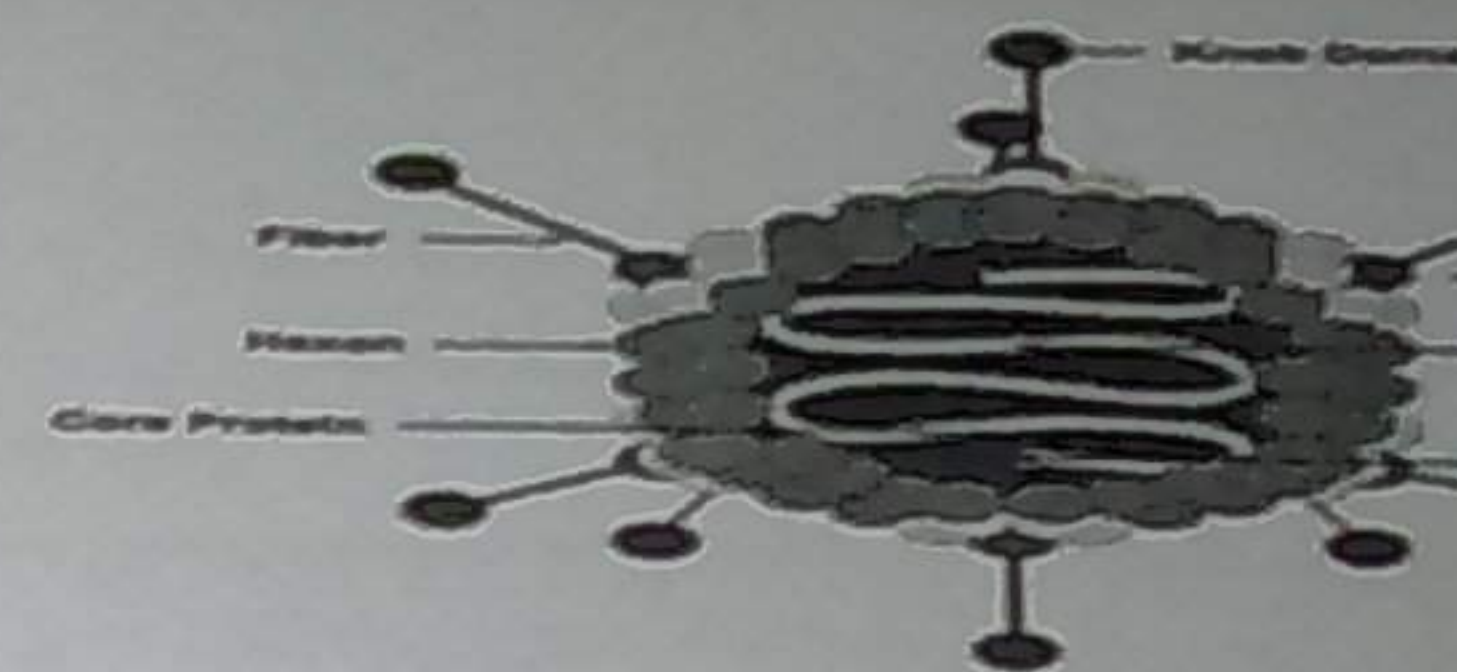


# Adenovirus

Genome  
Ds DNA

## Structure

Capsid : Icosahedral & carries fibers with knobs  
Attachment of virus Type specific Ag: 52 serotypes Heamagglutination  
Non enveloped



## Mode of transm.

## Pathogenesis

## Prevention

1-Droplet

A-Replicate in epithelium of:

1-RT

i-Avoid overcrowding

ii.Live attenuated oral vaccine for military  
( ceased in 1996)

2-Contam. eye equipments  
& Direct contact

2-Eye

iii.Adequate sterilization of solutions &  
equipments used in eye examianation  
iv.Chlorination of swimming pools

3-Fecooral

3-GIT&UT

v.Proper hand hygiene

B-Virus may invade blood  
In early stage of ds

C-Most inf.are asymptomatic  
Virus may remain latent for life in adenoids

## Laboratory diagnosis

### A-Specimen

Swabs : Throat , conjunctiva , rectum

Stools or urine

### B-Identification

Direct virus demonstration

Virus isolation

Serology : CFT

EM

Viral particle

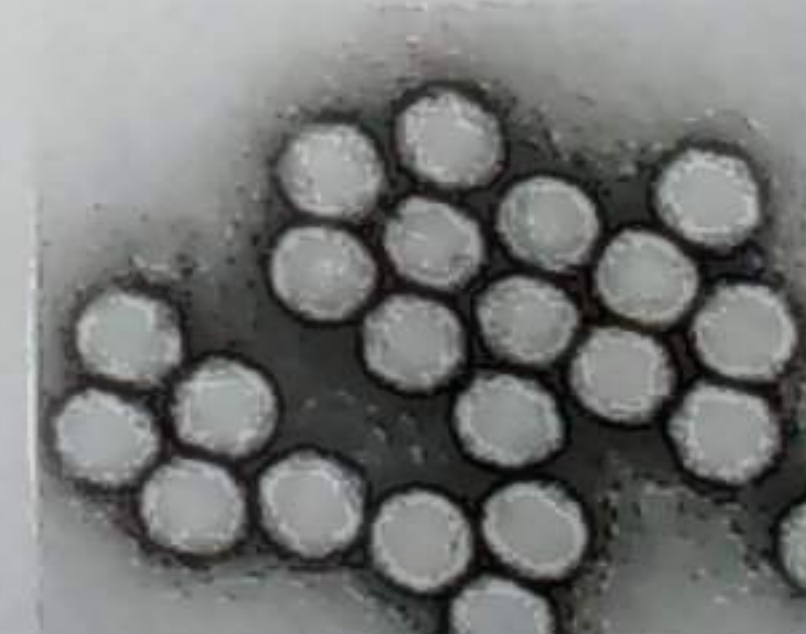
PCR

Viral DNA

On human epithelial cells (slow)

CPE : grape like rounded cells

Serotyping by HIT



Rising titer of IgG (4folds)

in 2 samples



# Diseases (acute & self limited)

## I-Respiratory & Eye diseases

### Respiratory ds

#### 1-Febrile respiratory ds (common cold)

Children: usual manifestation

Running nose, dry cough & pharyngitis



#### 2-Acute respiratory ds (ARD)

Military groups



Cough, pharyngitis → **Pneumonia**

#### 3-Pneumonia : in hospitalized children (nosocomial)

### Eye ds

#### 1-Acute pharyngoconjunctival fever (APC)

Children: Outbreaks due to insufficient chlorination of swimming pools



Pharyngitis & conjunctivitis



#### 2-Epidemic keratoconjunctivitis (EKC)

Adults: By contaminated eye instruments (highly infectious)



Conjunctivitis → **keratitis** → **corneal opacity**

#### 3-Conjunctivitis

## II-GIT & UT ds

GIT

**Infantile gastroenteritis**

By types 40 & 41

UTI : Hgic cystitis (reactivation of dormant virus or nosocomial spread)

Children (commonest cause)

Aged 5-15yrs & boys > girls

Kidney or BM transplantation

IS adults

AIDS

## III-Severe infection in IS pts

Transplant pts

**Pneumonia** (fatal)

**Hepatitis** in liver allograft

AIDS

**Gastroenteritis**



# Polyoma viruses

Ds DNA

Structure

Capsid :icosahedral

Non enveloped

## Members & Diseases

BK virus

JC virus

1-1ry subclinical inf. in childhood

Persist (latent) in healthy individuals

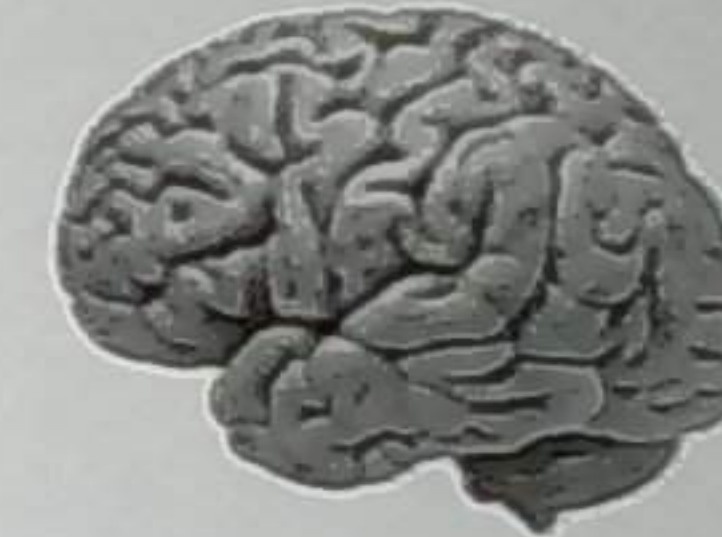
in *kidneys*

in *brain*

2-Reactivation in IS pts

*Nephropathy & rejection* of renal grafts

Progressive *multifocal leukoencephalopathy* → fatal



HHV8 ( Kaposi sarcoma associated herpes virus)

❖ Oncogenic with AIDS

❖ Diagnosis

*Kaposi sarcoma*

Body-cavity based *lymphoma*

PCR

Endothelial cell tumor

Viral DNA





## Essay Questions

- 1-Give an account on human papilloma virus as regards structure, ds produced and laboratory diagnosis.
- 2-Prophylaxis of human papilloma virus
- 3-Mention causative org. ,mode of transmission and clinical picture of : Condyloma accuminata ,dendritic ulcer of cornea and non immune hydrops fetalis
- 4-Discuss viral structure and laboratory diagnosis of cytomegalovirus.
- 5-Mode of transmission and pathogenesis of Varicella zoster virus
- 6-Describe laboratory diagnosis of herpes simplex virus.
- 7-Compare & contrast VZV &CMV as regards site of latency & mode of transmission
- 8-Mention specific laboratory tests used in diagnosis of infectious mononucleosis and their significance
- 9-Give an account on general characteristics of herpes viridae family
- 10-Laboratory diagnosis of infectious mononucleosis.
- 11-Describe pathogenesis of HSV 1& 2.
- 12- Give reason:
  - a. antiviral drugs don't eliminate latent stage in herpes infection.
  - b. Parvovirus B19 is a serious infection in pts with chronic hemolytic anemia
- 13-Mention the causative org. and mode of transmission of :
  - a.Shingles
  - b.Infectious mononucleosis
- 14-Mention the value of the following laboratory tests:
  - a. Monospot test in diagnosis of infectious mononucleosis.
  - b. Tzank smear in diagnosis of Herpes simplex.

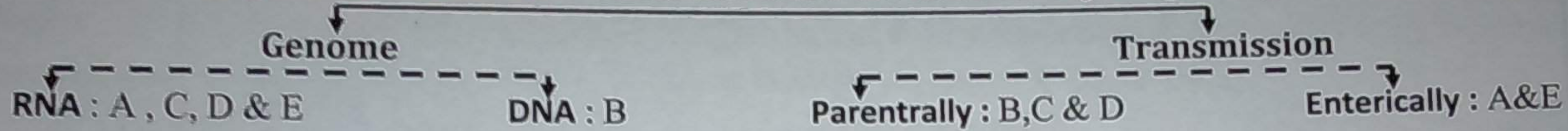


# **Virology 3**

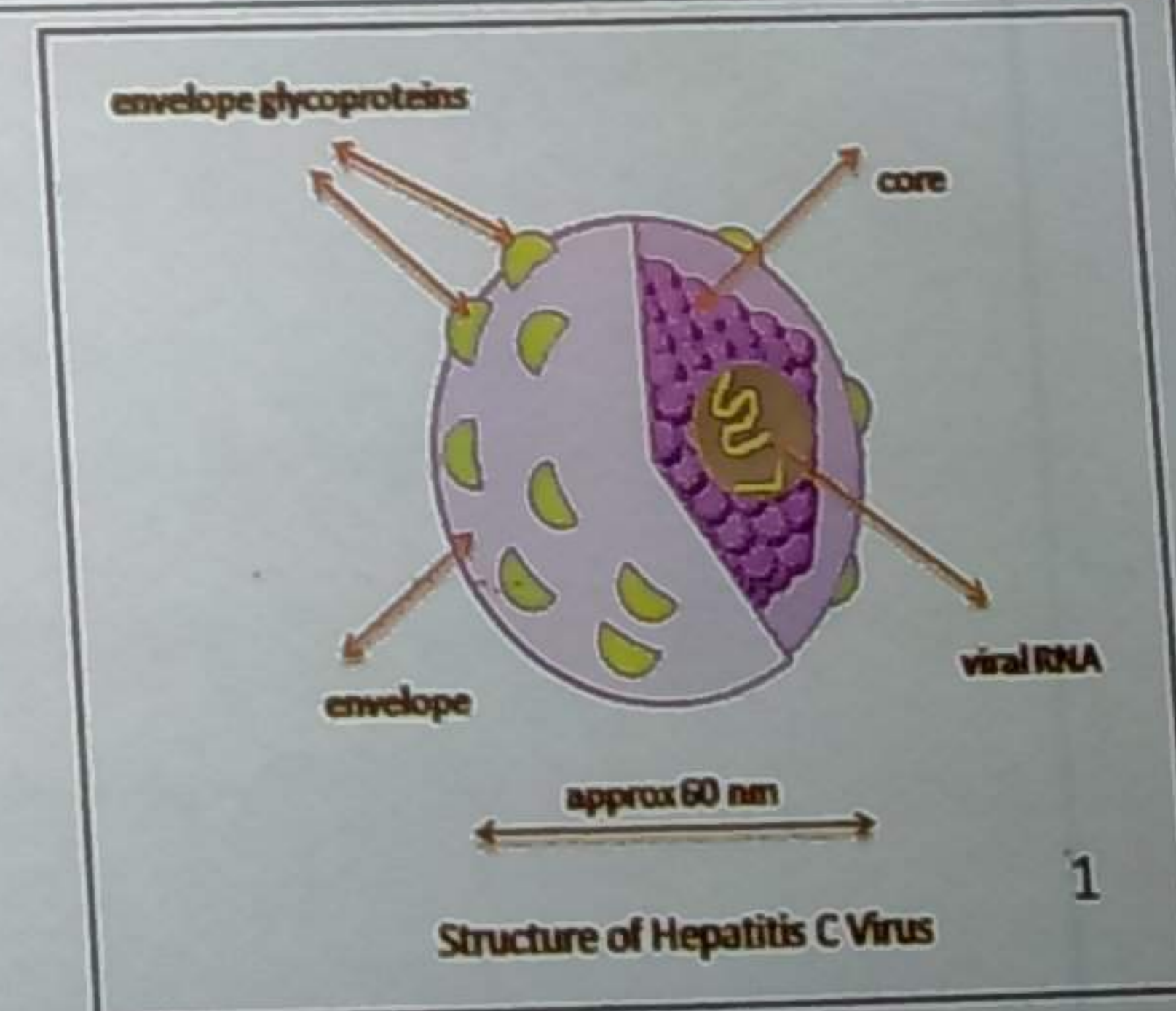
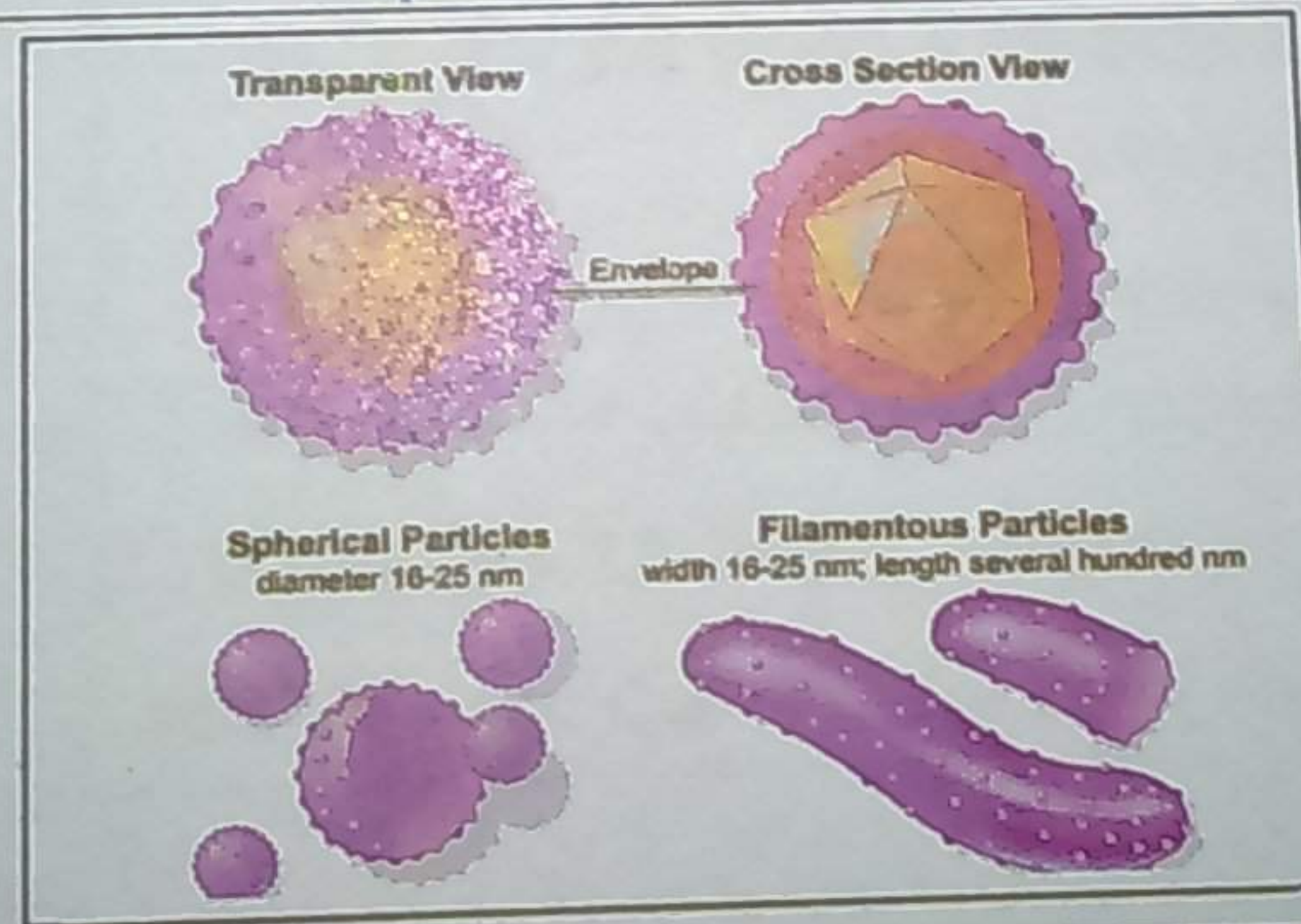
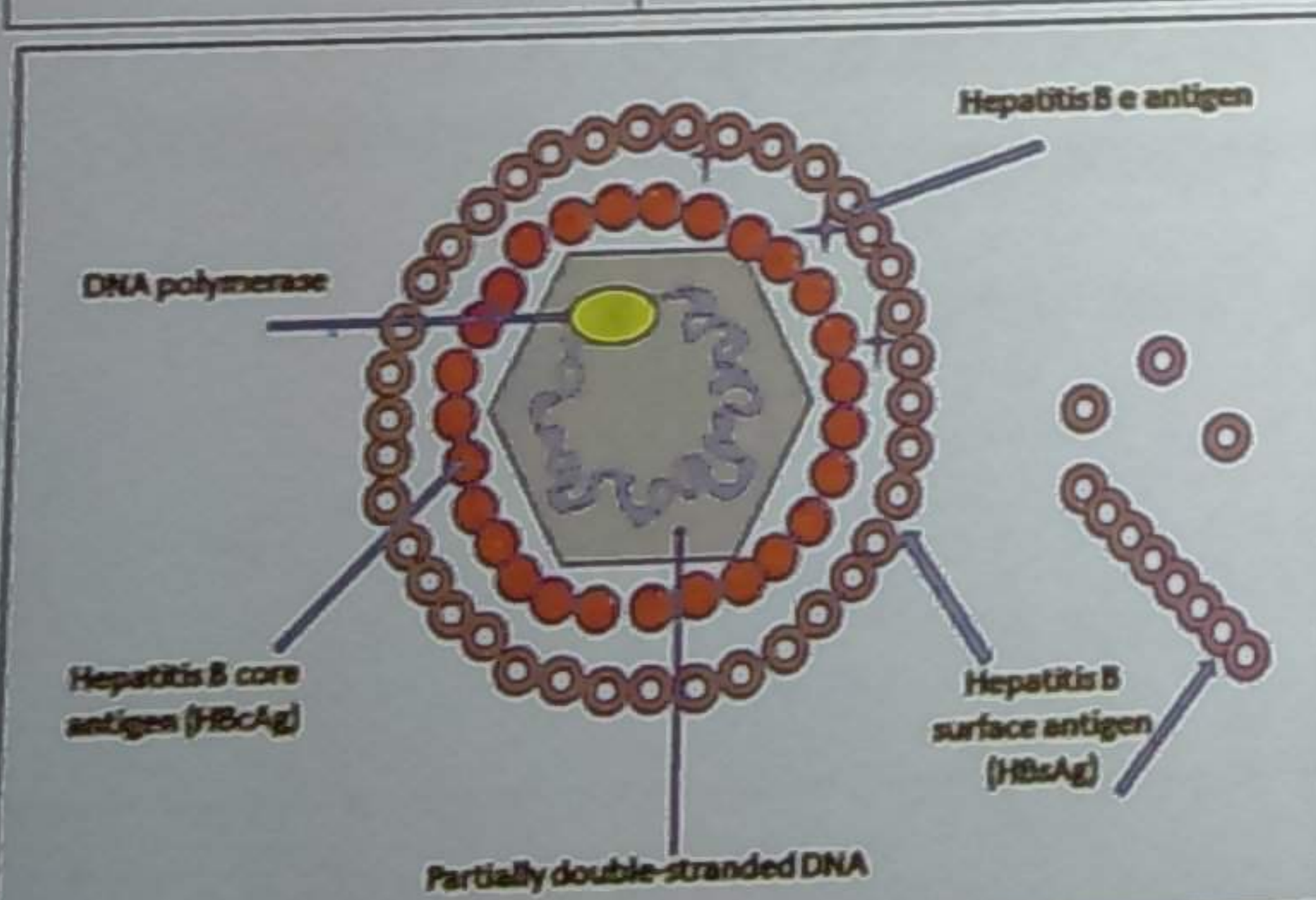
**Hepatitis Viruses**  
Hepatitis Viruses



## Hepatitis viruses : Viruses that infect the liver as 1ry target organ



	HBV	HCV
<b>Structure</b>		
A-Family	Hepadna viruses	Flavivirus
B-Core	1-Partially DS DNA 2-DNA polymerase 3-Core Ags : c Ag & e Ag	1 - SSRNA + ve sense 2 - 6 genotypes : <u>type 4</u> is predominant in Egypt
C-Capsid	Icosahedral	
D-Envelope : Host derived lipid bilayers	<p style="text-align: center;"><b>1. S Ag</b></p> <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;">             i . Attachment of virus ↓ Vaccine preparation           </div> <div style="text-align: center;">             ii . Presence of virus ↓ Diagnosis           </div> </div> <p style="text-align: center;"><b>2 . 3 forms of HBV</b> are detected in pt serum</p> <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;">             Complete virion ↓ <b>Dane particle</b> </div> <div style="text-align: center;">             Secreted S Ag without DNA • Spherical • Filamentous           </div> </div>	Carries viral Ag





	HBV	HCV
<b>Modes of transmission</b>	<b>1 - Parentrally</b> ( injured skin &MM) : blood & Blood products,sharing razors or toothbrushes <b>2 - Perinatally</b> : in uterus & during birth <b>3 - Sexual intercourse</b> <b>4-Organ transplantation</b>	
<b>Pathogenesis</b>		
<b>A-Entry &amp;spread</b>	<b>1-Enter &amp; spread by blood</b> to liver → Multiplication in hepatocytes <b>2-No CPE</b> : infected cells are damaged by <b>CTLs</b>	
<b>B-Fate</b>	15% of pts become <b>chronic</b> carriers (S Ag in blood ≥ 6 ms)	85% of pts become <b>chronic</b> carriers
<b>Chronic carriers</b>	<b>1 - Asymptomatic</b> mostly <b>2 - Chronic active hepatitis</b> → cirrhosis → <b>liver failure</b> and /or <b>HCC</b>	
<b>Immunity</b>	Anti S → life long immunity	
<b>Cl.picture</b>	Serum Hepatitis	Non A non B hepatitis
<b>A - IP</b>	1.5 m-6 ms ( Symptoms are <b>more severe</b> )	2 ws-6m ( <b>80%</b> of inf.are <b>asymptomatic</b> )
<b>B - S &amp; S</b>	<b>1- Fever, anorexia &amp; vomiting</b> <b>2- Jaundice</b> ,dark urine & pale stools	
<b>Treatment</b> ( chronic cases)	<b>1 - α interferon</b> <b>2 - Lamivudine</b> : nucleoside analogue	<b>1- α interferon + Ribavirin + Sofosbuvir (sovaldi):</b> ⊖ viral RNA polymerase <b>2-Harvoni :</b> <b>Sofosbuvir + Ledipasvir</b> (⊖ NS5A protein important in replication) • <b>Duration</b> :12-24 ws ( depends on viral count,genotype & cirrhosis) • <b>Monitoring: Quantitative PCR</b> ( 4ws,end of ttt,12ws after completion)



# Laboratory diagnosis of hepatitis B

**I - Non specific tests :** Marked ↑ in liver transaminases & bilirubin

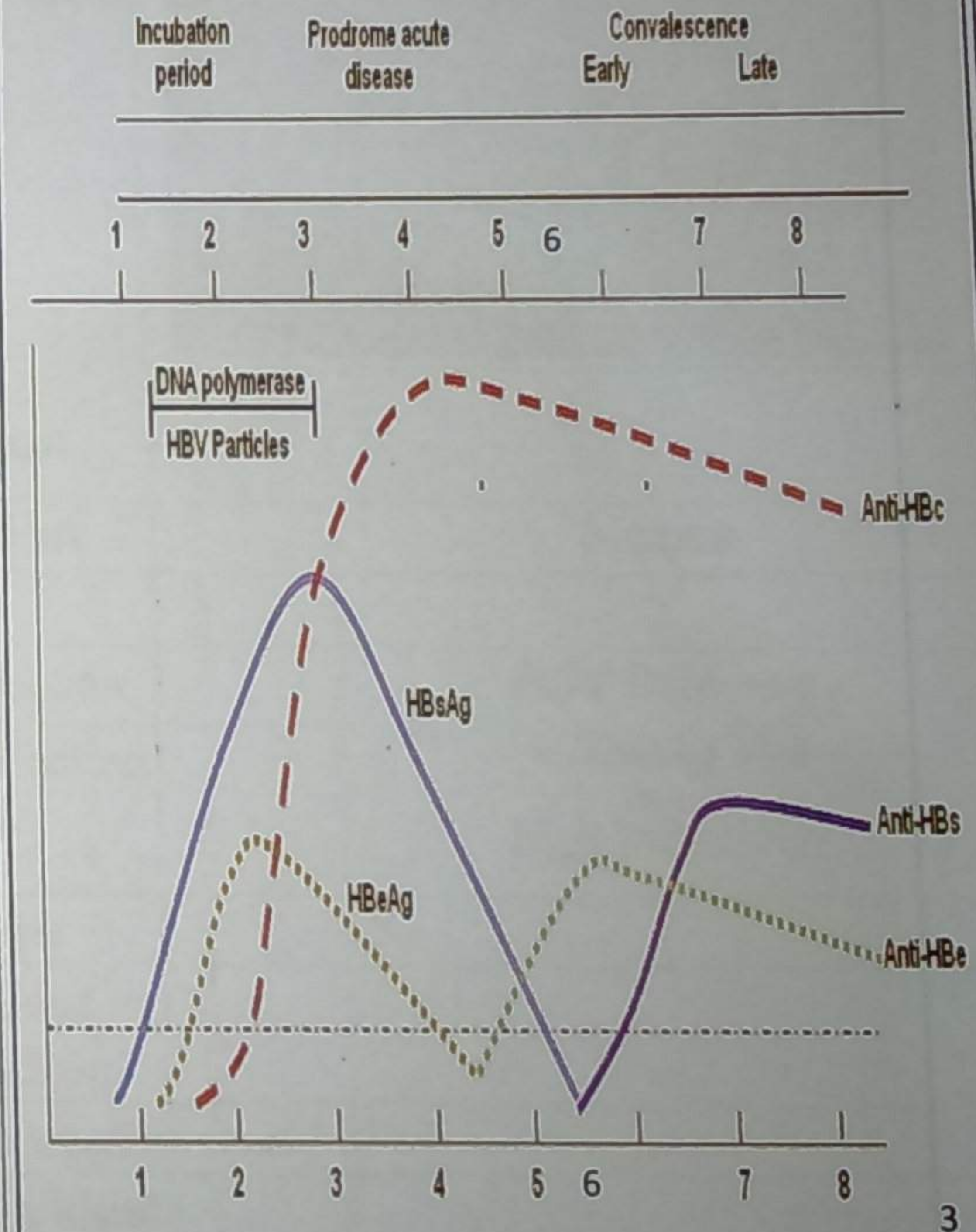
## II - Specific tests

**A-Hepatitis B panel :** in serum

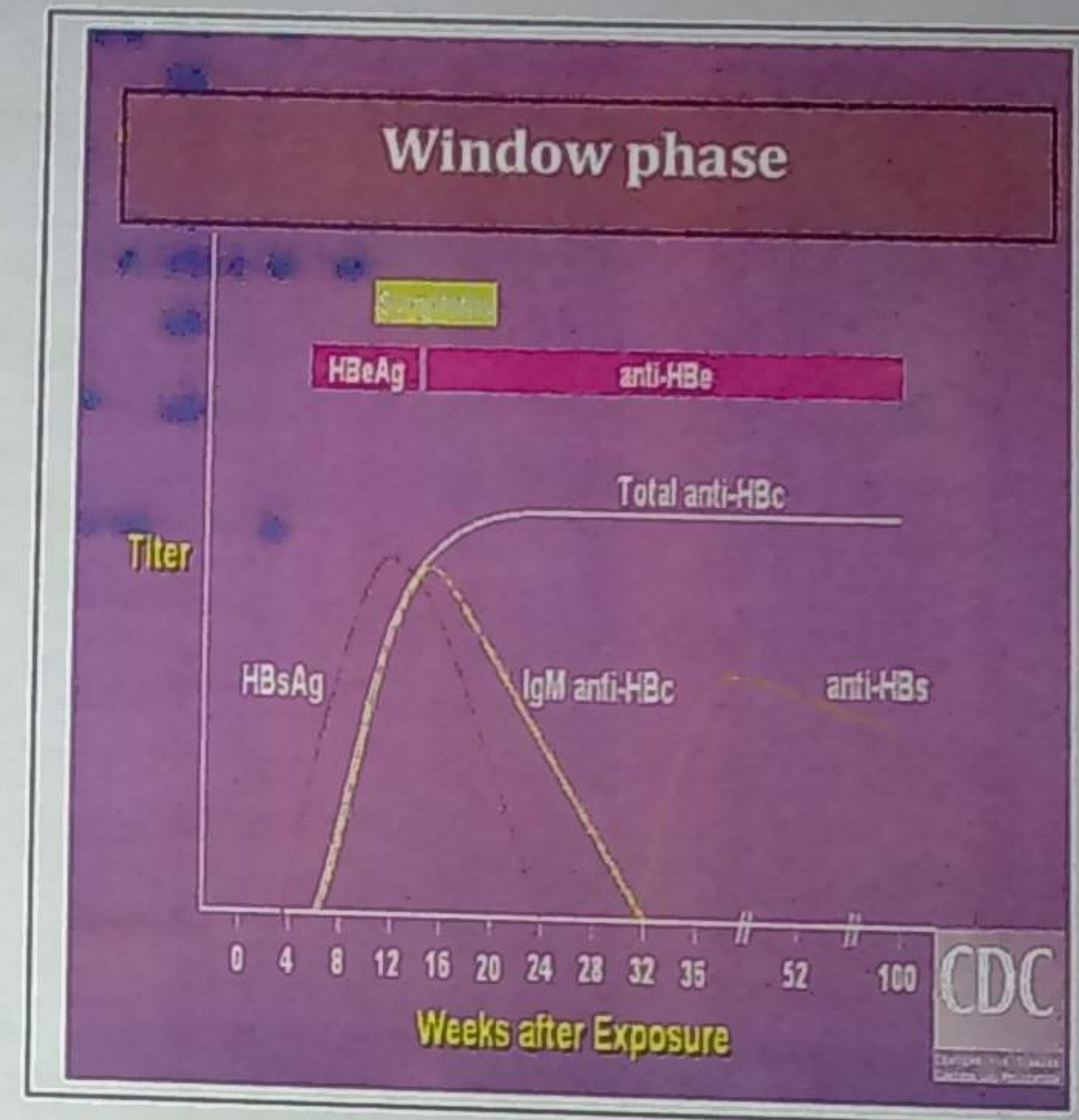
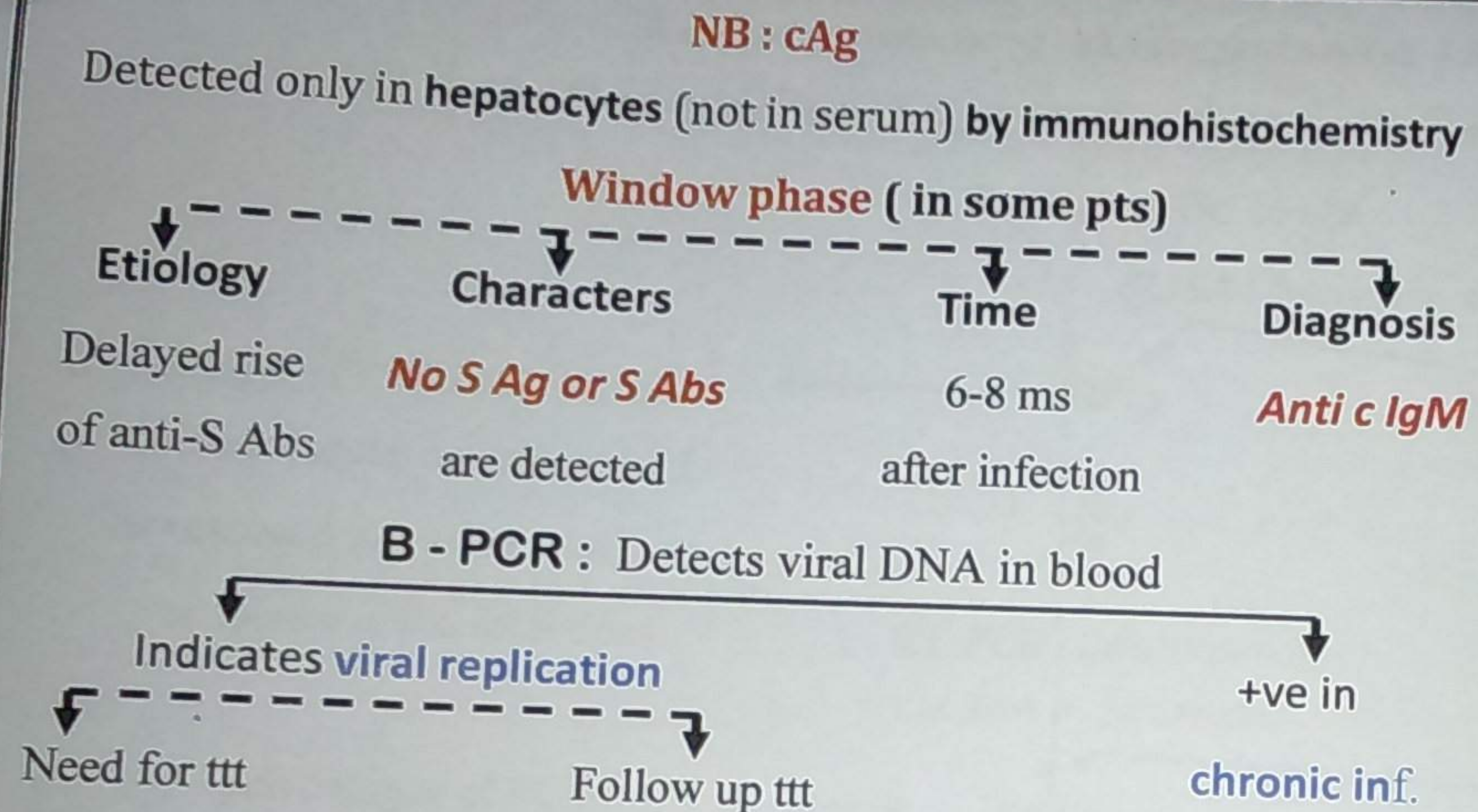
Detection of HB Ags (by direct ELISA) & HB Abs (by indirect ELISA) in serum

Marker	Time of detection	Significance	
<b>1-sAg</b>	1 <sup>st</sup> m (I P) → ↓ in 3 ms Disappears after 6 ms except in chronicity	<i>i.Acute</i> inf.	<i>ii.Chronic</i> inf.
<b>2-sAb</b>	After disappearance of S Ag ↓ For life	<i>i.Resolution</i> of inf.	<i>ii.Immunity</i> against reinf.
<b>3-cAb</b>			
<b>a..IgM</b>	Clinical onset ↓ Disappear after 6ms	<i>i.Acute</i> inf. (with SAg)	<i>ii.Window phase</i> (without SAg)
<b>b.IgG</b>	After disappearance of IgM ↓ For life	<i>i.Chronic</i> inf. (with SAg)	<i>ii.Past</i> inf. (without SAg)
<b>4-eAg</b>	I P ↓ Througout acute illness	<i>High infectivity</i> of pt ( <i>best marker</i> ) ↓ Its disapp. is a good prognostic sign	
<b>5-eAb</b>	After disapp. of eAg	<i>i.Low risk</i> of transmission	<i>ii.Recovery</i>
Persistence of eAg & absence of eAb indicate <i>chronic active hepatitis</i> → need for ttt			

HEPATITIS B PROFILE







### HBV Panel interpretation

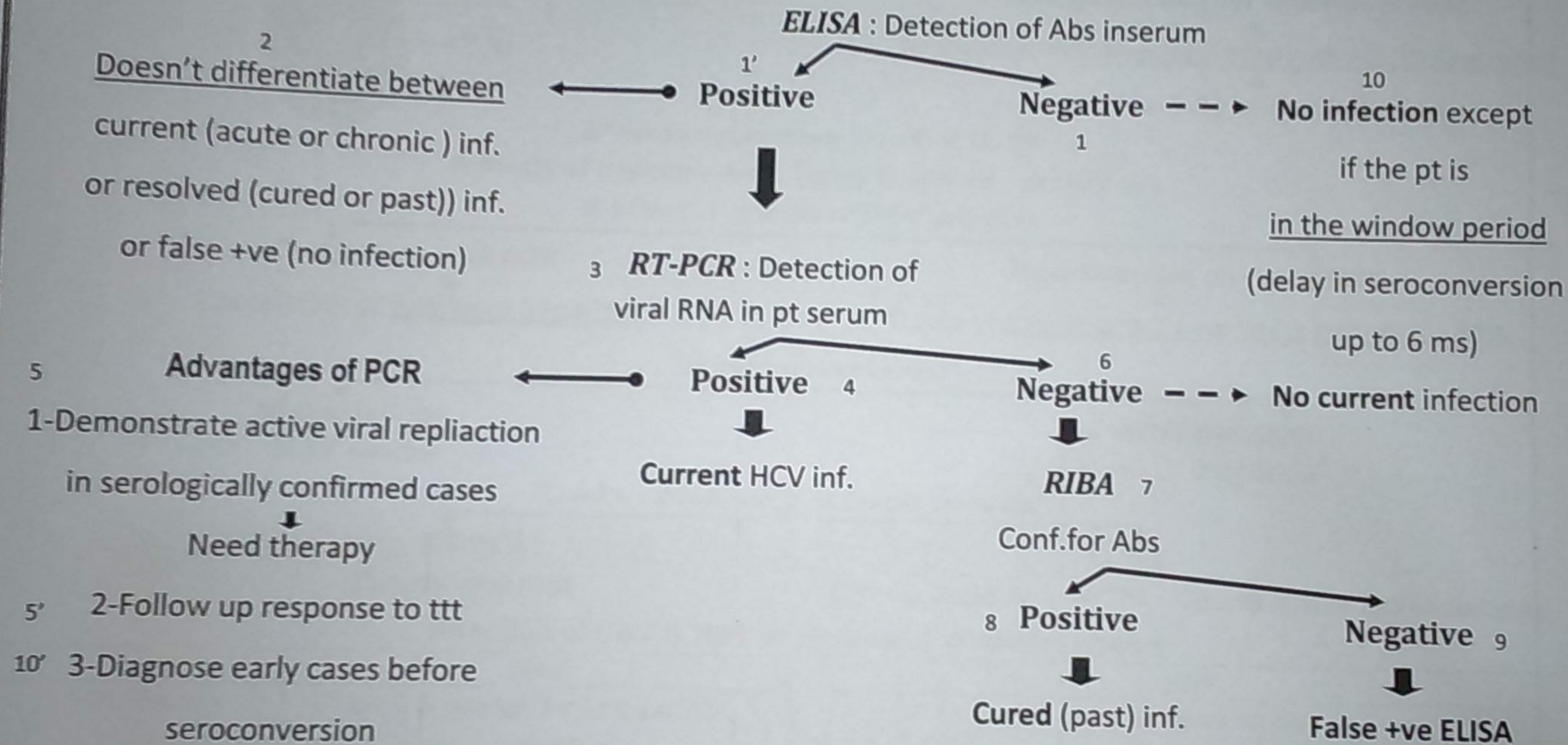
Test				Interpretation	Notes
HBs Ag	HBcIgM	HBcIgG	HBsAb		
+ve	+ve	-ve	-ve	Acute HBV infection	HBV DNA +ve + HBeAg +ve ↓ high infectivity
+ve	-ve	+ve	-ve	Chronic HBV infection	
-ve	+ve	-ve	-ve	Window phase	
-ve	-ve	+ve	+ve	Immune person due to previous infection	
-ve	-ve	-ve	+ve	Immune person due to vaccination	
-ve	-ve	-ve	-ve	Susceptible individual	



## Laboratory diagnosis of HCV

I - Non specific tests : Marked ↑ in liver transaminases & bilirubin

### II - Specific tests



### Disadvantages of PCR

Doesn't differentiate between  
acute (recent) & chronic inf.

### ■ Screening blood donors in blood banks :

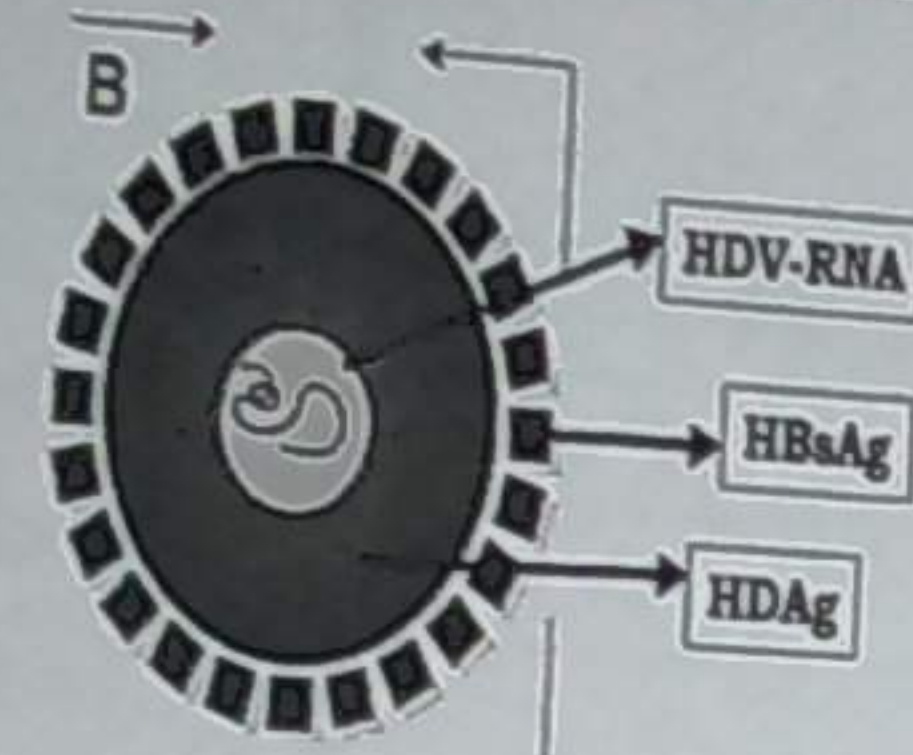
Combined Ab testing & Ag detection or RT PCR is recommended to  
avoid missing blood donors in window period



# Hepatitis D Virus

## Virus structure

SS RNA :  
-ve sense



Delta Ag

Defective virus

Lack gene coding for envelope protein

Replication only in cells infected with HBV(helper virus)

Use **S Ag** as envelope protein

## Pathogenesis & Cl.P

A-Mode of transmission, Entry & spread : as HBV (E).

B-Effect : ↑ severity of HBV infection

Coinfection with HBV

↑ possibility of fulminant hepatitis

Superinfection on top of HBV

↑ rate of chronic active hepatitis & cirrhosis to 80%

## Prevention

of coinfection  
HBV vaccine

of superinfection  
Avoid IV drug abuse

## Laboratory diagnosis

RT PCR

Detects **viral RNA**

ELISA

Detects **Delta Ag**

Detects **IgM or IgG to Delta Ag**

Reaction of HAV & HBV to physical & chemical agents

	HAV	HBV
1-Survive in	i.H <sub>2</sub> O & sewage for long periods ii.At 4C	i.Dried blood for ws ii.Environmental surfaces for 7 days at 25C
2-Resistant to	i.Heat at 60C for 1 hr ii.Extremes of pH:3(gastric acidity) iii.Lipid solvents (70% ethanol)	i.Heat ii.pH
3-Susceptible to	i.1% Na hypochlorite & 2% glutaraldehyde ii.Ethanol (70%) iii.Heating at 100C for 1 hr or autoclave	



Family & Structure	<b>HAV</b>		<b>HEV</b>	
	1-Picornavirus : Hepatovirus genus		Related to <i>Calici</i> viruses	
Modes of transmission	2-SS RNA : +ve sense		3 - 1 serotype	
	4 - Capsid : icosahedral		5-Non enveloped	
Pathogenesis	Feco-oral : ingestion of contaminated food & H <sub>2</sub> O ( not by blood due to low viremia )			
A - Entry & spread	Water -borne epidemics			
B - Fate	1-Ingestion → 1 <sup>st</sup> multiplication in <i>GIT</i>			
	2- Spread by blood to liver → Multiplication in hepatocytes			
	3-No CPE : infected cells are damaged by <i>CTLs</i>			
Immunity	1- Clearance of inf. → repair of damage & recovery			
	2-NO : chronicity, carriers or carcinoma			
Cl. picture			High mortality in <i>pregnant</i> ♀	
	✓ IgM : Onset of jaundice			
A-IP	✓ IgG : 3ws later → lifelong imm.			
B- S & S	Infectious hepatitis		Enteric Non A non B hepatitis	
Treatment	2 ws ( Most inf. are asymptomatic)			
	Jaundice, dark urine & pale stools ( <i>Children</i> are the most frequently affected )			
Laboratory diagnosis	No antiviral drugs			
	I- Non specific tests : Marked ↑ in liver enzymes & bilirubin			
	II- Detection of Abs in serum by ELISA			
	1.IgM indicates <u>recent</u> infection			
	2.IgG indicates <u>past</u> infection			
	IgG may indicate vaccination			
	C - RT-PCR : detects viral RNA			
	D - EM : Detects <u>virus</u> in stools			
E - RIA : Detects <u>viral Ag</u>				

7



## Prevention of hepatitis viruses

### I - Hygienic measures (behavior modification)

HAV & HEV	HBV & HCV
<p>Most important</p> <p>1-Good hygiene</p> <p>2-Chlorination of H<sub>2</sub>O</p>	<p>1-Avoid parenteral transmission by</p> <p>Proper exam. of blood &amp; blood products</p> <p>Proper sterilization &amp; standard precautions</p> <p>Avoid sharing of needles &amp; razors</p> <p>No blood from any pt with hepatitis history</p> <p>2-Cesarian section : for chronic carrier pregnant ♀</p>

### II - Immunization

9

#### HBV

#### A - Active : vaccine

#### 1 - Preparation & administration

<p><b>Inactivated</b></p> <p>♣ IM: 1st dose</p> <p>↓ 6ms</p> <p>2<sup>nd</sup> dose</p>	<p>♣ S Ag produced in yeast by recombinant technique.</p> <p>♣ 3 doses : 0, 1 &amp; 6ms</p> <p>♣ IM : i. <u>Deltoid</u> : Children &amp; adults    ii. <u>Thigh</u> : newborn</p>
---	---

#### 2 - Indications

Children	<p>i. Routinely to newborns &amp; adolescents</p> <p>ii. High risk groups (frequently exposed to blood &amp; blood products)</p> <p>♦ Hemophilia</p> <p>♦ Hemodialysis</p> <p>♦ Health care workers</p> <p>• Dentists • Surgeons • lab. workers</p>
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#### B - Passive : Post exposure prophylaxis

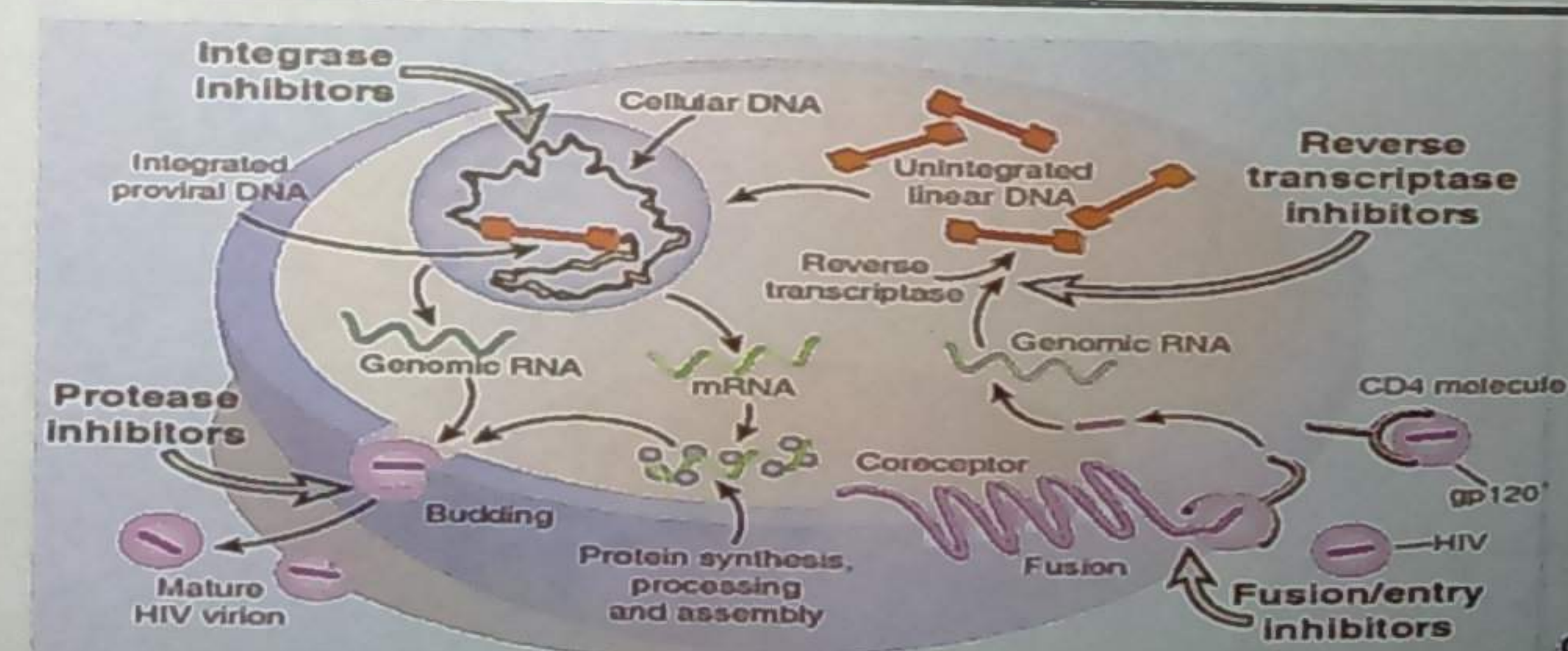
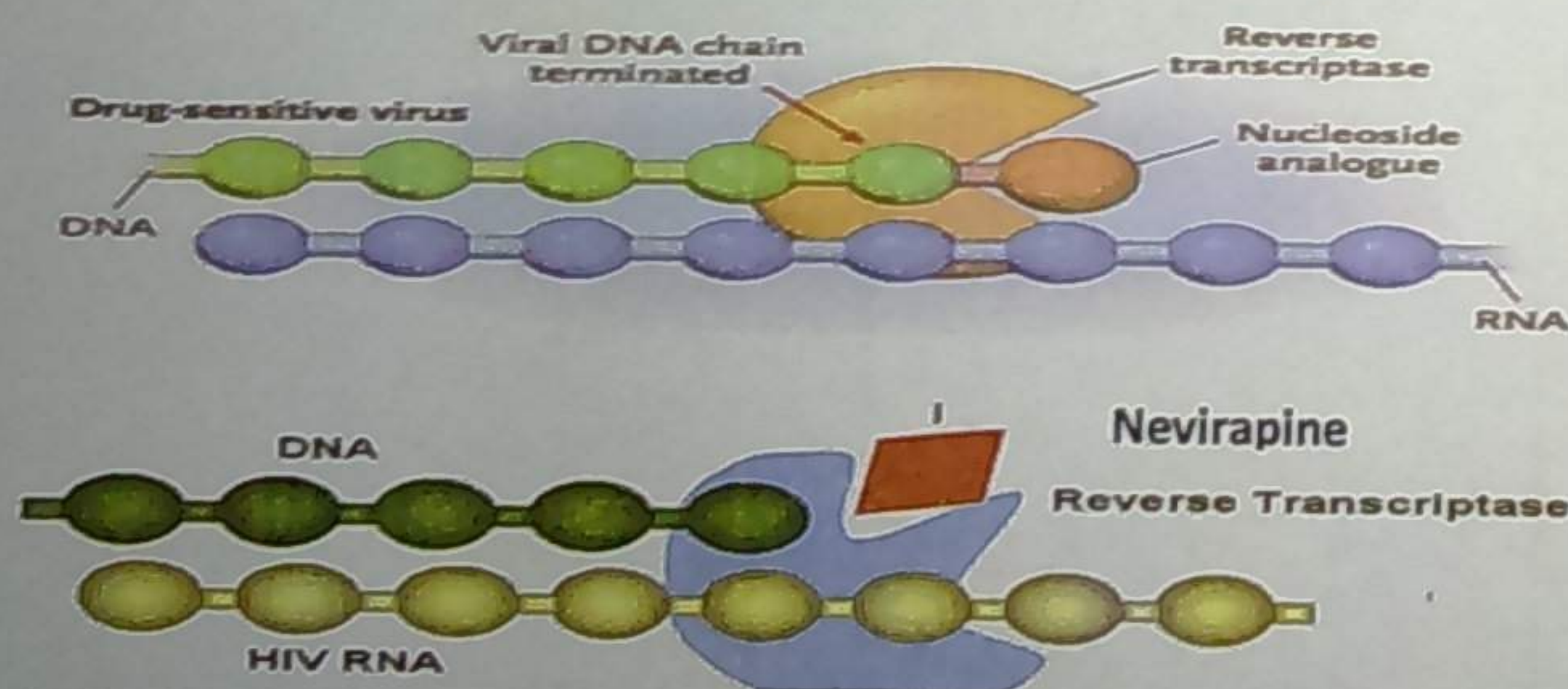
HAV Igs	<p>1- HBV Igs (anti S)</p> <p>Accidental exposure to S Ag +ve blood : Needle prick or sharp injury</p> <p>Newborn to S Ag +ve mother</p> <p>2- Vaccination is given simultaneously at a separate site</p>
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8



# Antiviral chemotherapy

Mechanism of action	Examples	Uses : TTT of
<b>I-Drugs affecting attachment&amp;penetration (Fusion inhibitor)</b> Blocks fusion between virus & CM	Fuzeon	HIV
<b>II-Drugs affecting uncoating</b> Blocks virus uncoating	Amantadine & Rimantadine	Prophylaxis & ttt of influenza A
<b>III-Drugs affecting nucleic acid synthesis</b>	Acyclovir ♦ Gancyclovir	• HSV&VZV ♦ CMV
<b>1-Nucleosides analogues</b> ⊖ DNA polymerases → ⊖ NA replication		
<b>2-Reverse transcriptase (RT) inhibitors</b> i. Nucleosides analogues : ⊖ synthesis of proviral DNA ii. Non nucleosides analogues: binds directly to RT	• Azydothymidine (AZT) & Dideoxyinosine(DDI) [less toxic] ★ Lamivudine ✓ ♦ Nevirapine	• HIV ★ HIV & HBV ♣ HIV
<b>3- Interference with mRNA (Both DNA&amp;RNA Viruses)</b>	Ribavirin	HCV & RSV
<b>IV-Protease inhibitors</b> ○ viral protease required at late replication to form mature virion → Non infectious virus	Indinavir	HIV
<b>V-Drugs affecting release: Neuraminidase inhibitors</b> ⊖ virus release from infected cells ➡ ↓ viral spread & limits inf.	Zanamavir & oseltamivir ( inhalation )      ( oral )	TTT of Influenza A&B viruses





# **virology 4**

**Enveloped RNA**

Enveloped RNA



# Enveloped RNA viruses

Respiratory			Zoonotic		Retroviruses
Myxoviruses	Rubella	Corona	Rabies	Arbo	HIV
Local or systemic	♦ Systemic ♦ Congenital	Local			

## Myxoviruses

(Myxo = affinity to mucin)

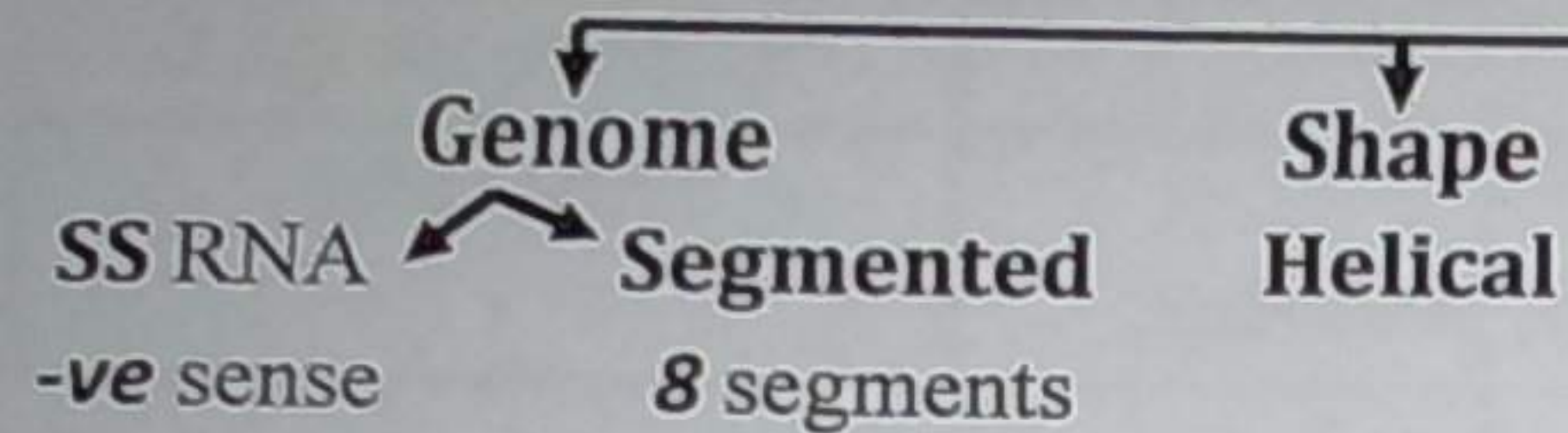
	Orthomyxoviruses	Paramyxoviruses
1-Members	Influenza V : local	i.Parainfluenza V & Respiratory syncytial V: local ii.Mumps V & Measles V: Systemic
2-Size	Smaller	Larger
2-RNA genome	Segmented	Non segmented
3-Genetic reassortment & Antigenic variation	Very common	Very rare



# Influenza Viruses

## Structure, Ags & Classification (1)

### A - Nucleocapsid



### Ags & Classification

2 type specific protein Ags (core Ags)

Nucleocapsid Ag & Matrix (M) Ag → Divide V into 3 serotypes: A, B & C

### B - Envelope

Contains 2 projecting glycoprotein spikes: HA & NA

### 1-Classification

Subtype (strain) specific Ags (Major Ags) → Divide type A into strains → Each one is named according to its type of HA & NA  
e.g H1N1 & H3N2 (there are 16 H & 9 N)

### 2-Functions

Haemagglutinin (HA)	Neuraminidase (NA) (2)
1-Binds to host cell receptors → viral entry ✓ Abs against it neutralize infectivity & prevent ds	1- Cleaves neuraminic acid of infected cell → viral release ❖ Its Abs ↓ viral release & spread → reduce ds
2-Haemadsorption & Haemagglutination of animal RBCs	2-Degrade protective mucin in RT → Binding of HA to receptors

### Antigenic variation

	Antigenic drift (3)	Antigenic shift (4 & 5)
1-Type	Type A & B	Type A only: Wide host range; infects both human & animals: Pigs, aquatic birds & chicken
2-Etiology	Spontaneous point mutation	Genetic reassortment: 2 viruses of different strains infect a single cell (In pigs: susceptible to avian, human & swine strains) Gene segment coding for HA or NA in one strain is replaced by another seg. from the other strain
3-Result	Minor change in a.a. sequence of HA or NA → Annual change of vaccine	New strain with new HA or NA No one is immune as it isn't covered by annual vaccination → Epidemics & pandemics
4-Time	Ongoing: every yr or few yrs	Every 10-20 yrs



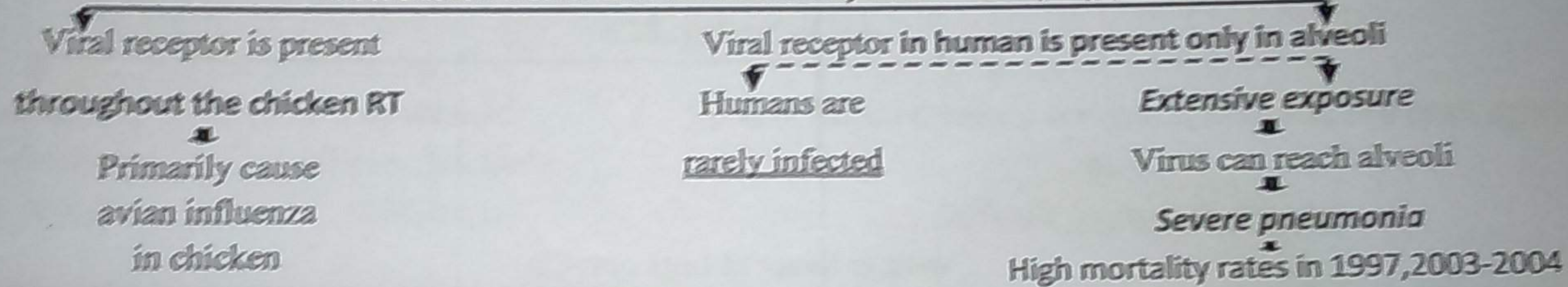
Types of Influenza virus			
	Type A	Type B	Type C
1-Host range	Human & animals.....	Only human	
2-Antigenic variation	Shift & drift	Drift only	Stable
3-Severity	Severest Epidemic & pandemic every 10-20 yrs	Less severe Outbreaks only	Doubtful pathogenicity

### Avian Influenza virus in humans

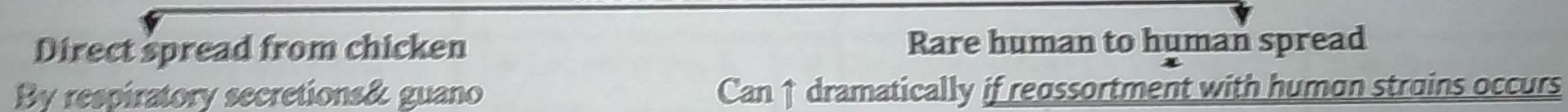
#### I-H5N1

#### Pathogenesis & Outbreaks

Infect chicken & other birds more effectively than humans (Why?)



#### Mode of transmission

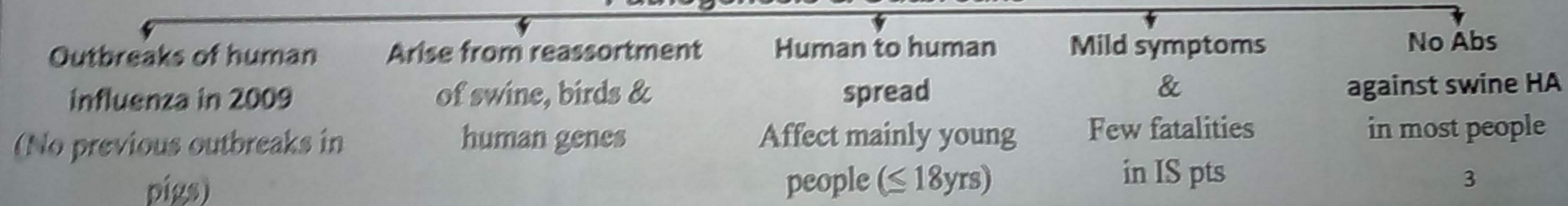


#### II-H7N9

Outbreak was restricted to China

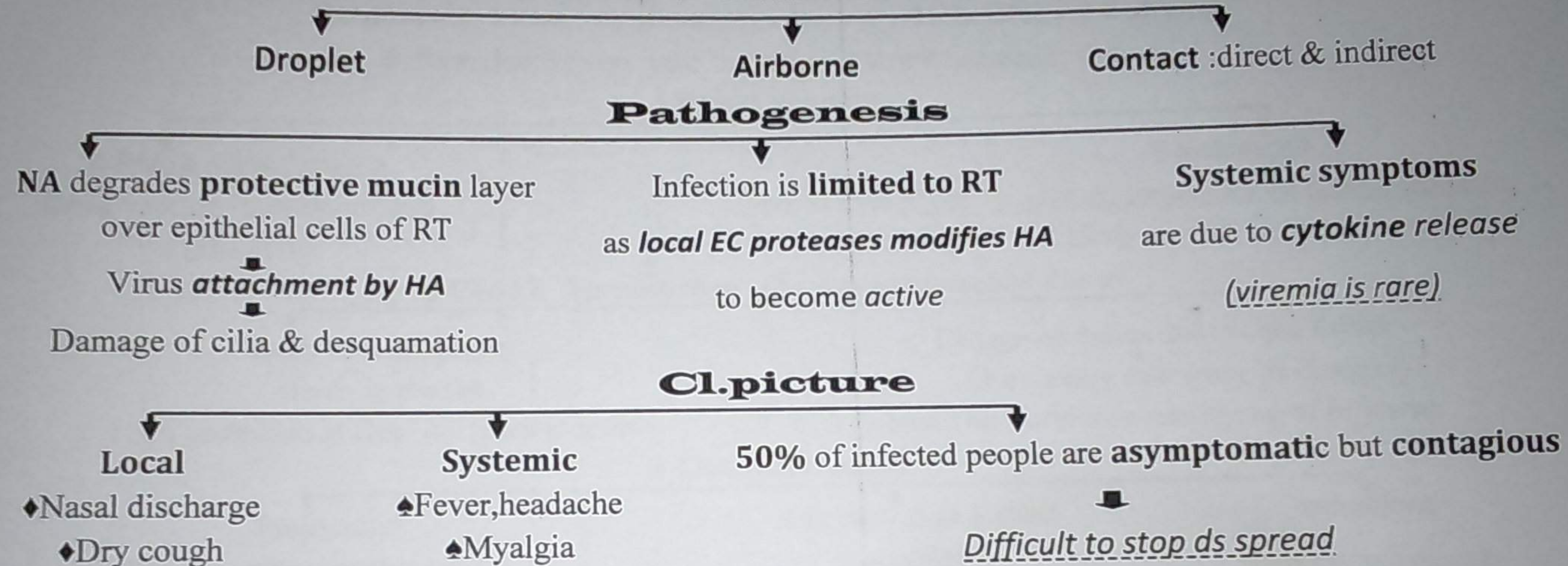
### Swine Influenza virus in Humans: H1N1

#### Pathogenesis & Outbreaks

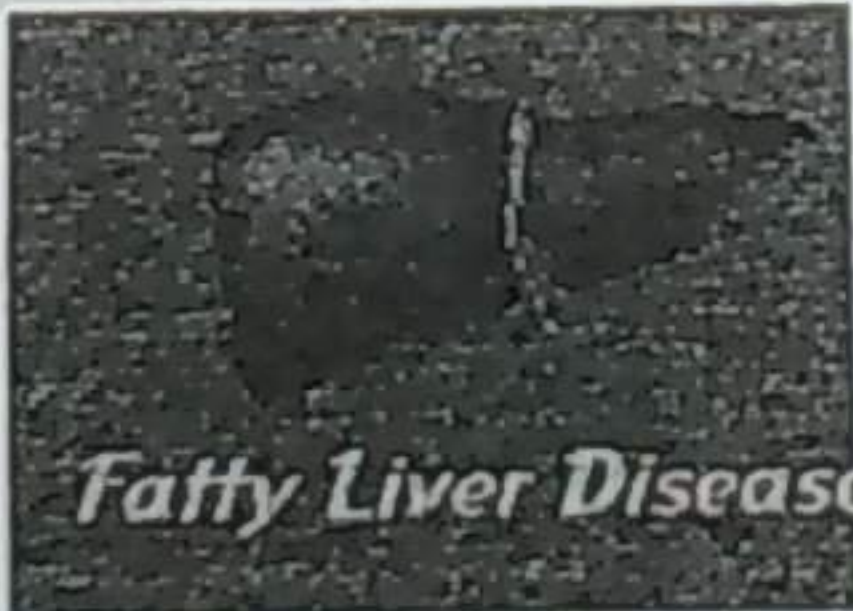





### **Modes of transmission of Human influenza** (Highly contagious)



## Complications

1-Pneumonia		2-Rye syndrome (rare)			
1ry influenza (Fatal)	✓ 2ry bacterial (most common) <ul style="list-style-type: none"> <li>☹ <i>S.aureus</i></li> <li>☹ Pneumococci.</li> <li>☹ H.influenza</li> </ul>	♣ Encephalitis & Hepatic necrosis  Following <b>Salicylate</b> intake <div>  <p>Fatty Liver Disease</p> </div>	♣ Causative virus <ul style="list-style-type: none"> <li>• Influenza A&amp;B</li> <li>• VZV</li> </ul>	♣ Age  Children & adolescents (2-16 yrs)          4	♣ Prevention  Avoid salicylate in children with <b>flu-like</b> <b>symptoms</b> <div>  <p>ASPIRIN</p> </div>

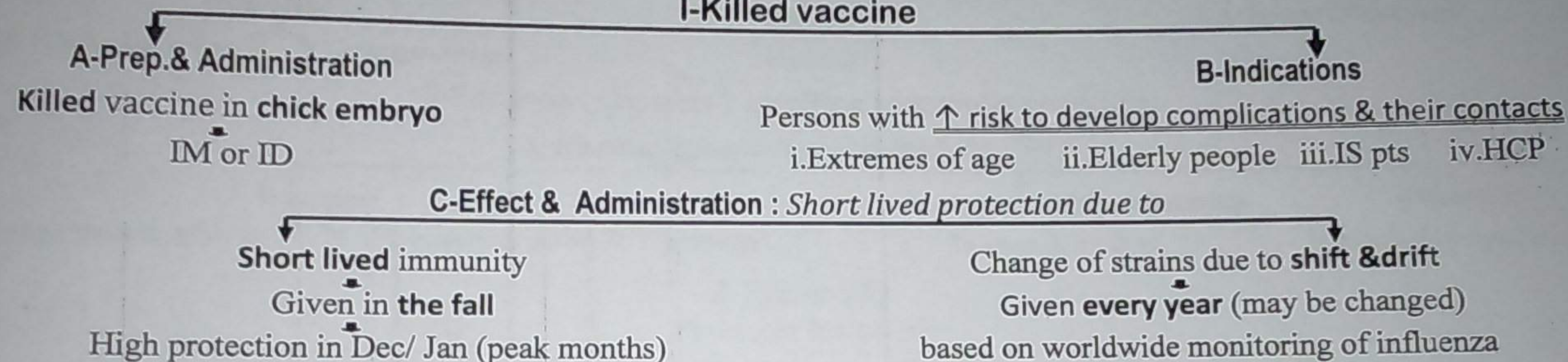


## Prevention & control by vaccines

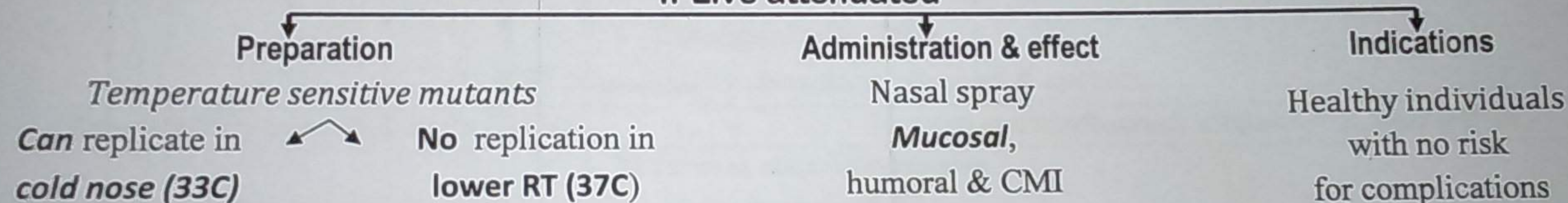
Quadrivalent vaccine : most recent isolates of H1N1, H3N2 + 2 B strains

→ Reformulated every year to contain current antigenic strains

### I-Killed vaccine



### II-Live attenuated



### III - Recombinant Vaccine

Inserting the *gene coding for HA* in a vector

■ Both inactivated & live attenuated vaccine become available against swine flu in 2009

■ There is *no human vaccine for H5N1*, but there is one available for avian species

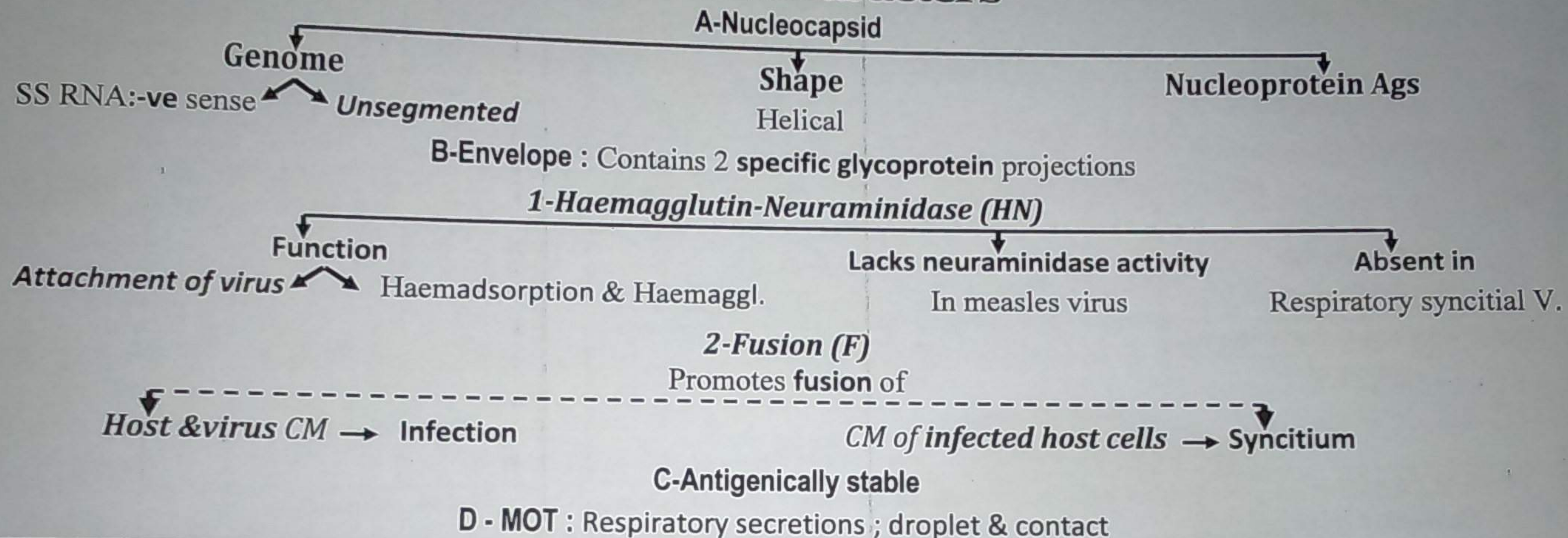
## Prevention & Treatment

	Amantadine & Rimantadine	Zanamavir & Oseltamivir
1-MOA	⊖ penetration & uncoating	⊖ neuraminidase → ↓ viral spread → ↓ duration of symptoms
2-Uses & Indications	Ttt & prevention of type A only • Swine & avian flu are resistant Vaccine is preferred for prophylaxis	Ttt only of type A & B (swine & avian flu are sensitive) ♣ Post exposure prophylaxis in non vaccinated elderly Must be taken within 48 hrs of symptoms



# Paramyxoviruses

## General Characters



Respiratory syncytial virus (RSV)

Human parainfluenza viruses 1,2,3&4 (HPIV)

## Virus structure

1-Nucleocapsid (E)

2-Envelope

F only (E)

HN & F (E)

## Pathogenesis & Cl.P

1-Upper RT ds : common cold like symptoms (repeated attacks)

2-Lower RT ds : Pneumonia & bronchiolitis

i. Especially in **elderly**: Pts with heart, lung & immune deficiency ds

ii. Very common in **infants < 1 yr of age**

The most common cause

The 2<sup>nd</sup> most common cause






3 -Croup (laryngotracheobronchitis) : by HPV1&2

## Treatment

•O<sub>2</sub> •Mechanical ventilation •Ribavirin aerosols



# Systemic Viruses

Family	Mumps virus	Measles virus	Rubella virus
Structure	Paramyxoviruses		Toga virus
1-Nucleocapsid	E		SS RNA +ve sense
2-Envelope	E		2 glycoproteins 1 Hemagglutinates RBCs
S & MOI	❖ Respiratory secretions & saliva : droplet and contact		
	✓ Urine	✓ Airborne ♦ Highly contagious ♦ Maximal infectivity before rash	✓ The only Toga virus not transmitted by arthropods
Pathogenesis & Cl. P	Epid. non sup. parotitis	Measles (rubeola)	German measles (post natal rubella)
A-Age affected	5-15 yrs	Younger age	As mumps
B-Initial replication & viremia	1-Nasopharynx	1-Upper & lower RT 2- Regional LNs → viremia → spread to multiple tissues	
D - Affected tissues	<b>1-Glandular tissues :</b> • Salivary glands <b>Parotitis</b>  • Pancreas • Testes & ovaries • Thyroid <b>2-Meninges</b> <b>Aseptic meningitis (mild)</b>	<b>1-Conjunctiva : Conjunctivitis</b> → photophobia <b>2-Oral cavity : Koplick's spots</b> • White dots inside cheek  • Before rash & disappear after its onset <b>3-Skin : Maculopapular rash</b> Etiology ← T cells attacking VIECs in small BVs → Site Face Exfoliation after 7 days 	<b>1-Cervical LN ++</b> Suboccipital & postauricular  <b>2-Skin</b> <b>Maculopapular rash</b> Face → trunk → extremities Disappear after 3 days 



	Mumps	Measles	Rubella
E-Immunity	1 serotype causing systemic inf.	Long lasting immunity by neutralizing IgG	Repeated attacks may occur
Complications	1-Glandular tissues ⊕ Orchitis Sterility in adults ⊕ Oophritis ⊕ Pancreatitis ⊕ Thyroiditis 2-Severe aseptic meningitis In adults	<div style="text-align: center;">Maternal Abs protect infant for 6-8 ms</div> <div style="display: flex; justify-content: space-around;"> <div>               1- Pneumonia                2ry bacterial pneumonia                (Most common)             </div> <div>               Viral giant cell pneumonia (rare but fatal)                With ↓ CMI             </div> </div> <div style="text-align: center;">2-Neurological (rare)</div> <div style="display: flex; justify-content: space-between;"> <div>a.Postinfectious encephalitis <u>Few days</u> after the rash disappear</div> <div>b.Subacute sclerosing panencephalitis <u>10 yrs</u> after initial inf</div> </div>	Postinfectious encep. <u>1w</u> after rash Recovery with no sequelae
<b>Prevention</b>			
I-Active immuniz.			
	<b>A - Monovalent vaccine</b>		
1-Preparation	Live attenuated → given SC		
	In chick embryo	In human diploid cell culture	
2-Effect	Long term immunity	10 yrs immunity	
3-Indications		i.Routinely to children	ii.Non pregnant adult females → Avoid pregnancy for 3ms
	<b>B - MMR vaccine</b>		
1-Preparation	3 live attenuated viruses → SC 2 doses		
	a.1 <sup>st</sup> : children at 12 ms (no strong IR if given earlier)    2 <sup>nd</sup> : at 4 yrs (or 4 ws after 1 <sup>st</sup> )		
2-Contraindications	<div style="display: flex; justify-content: space-around;"> <span>i.IS pts</span> <span>ii.Pregnant ♀</span> </div>		
II-Passive immunization	By human Igs Within 1 w of exposure to inf.		
	<div style="display: flex; align-items: center;"> <div style="margin-right: 10px;">               i.IS pts }                ii.Pregnant ♀ }             </div>             (vaccine is contraindicated)           </div>		



# Congenital rubella syndrome

## Mode of transmission & pathogenesis

Maternal viremia (1<sup>st</sup>ry inf.) during pregnancy

↓  
Infection of fetus

↓ fetal cell growth rate without destruction

↓  
Hypoplasia of organs

Extent of teratogenic effects depends on **timing of fetal infection**

In 1<sup>st</sup> 18 ws → **most critical**

After 18 ws → Uncommon defects

### CLP

Transient symptoms

Growth retardation

Anemia

Permanent defects

Microcephaly

Cataract

Deafness

Congenital heart ds

## Laboratory diagnosis

A-During pregnancy

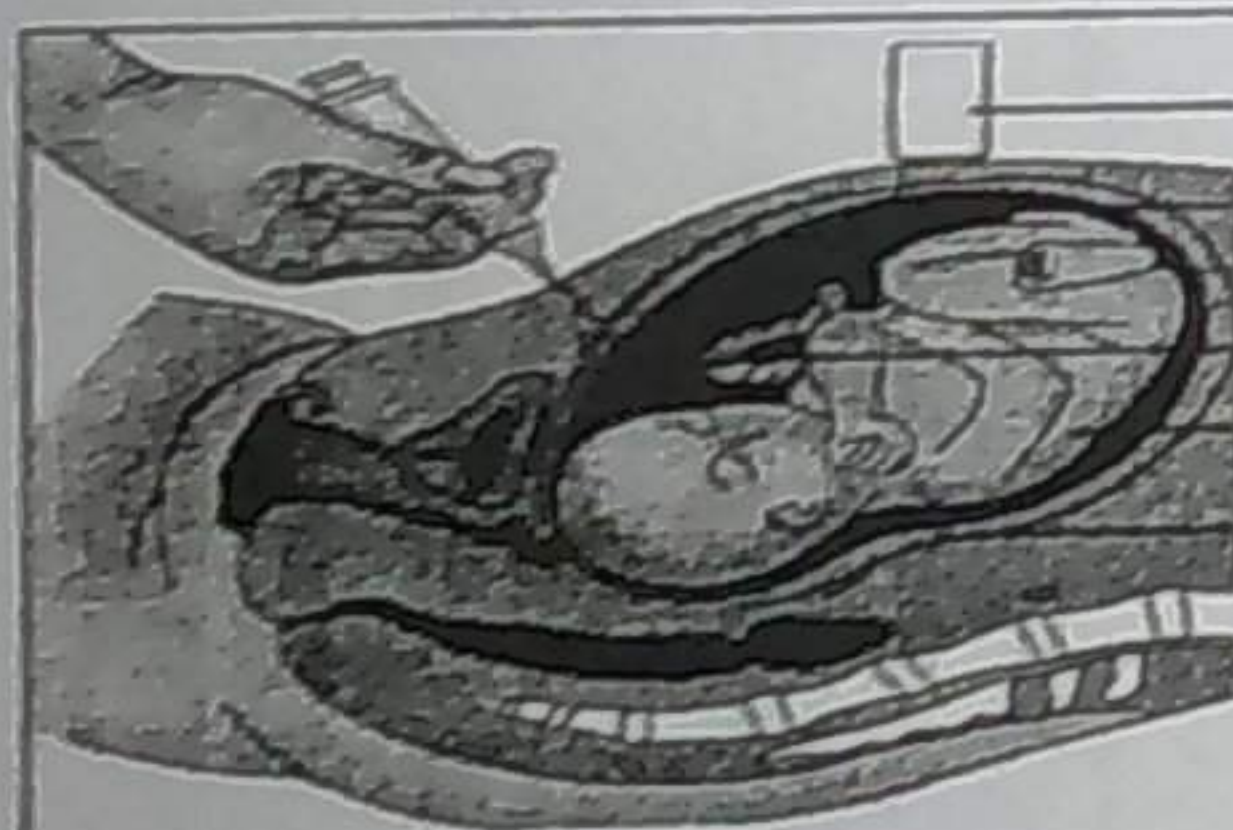
1<sup>st</sup> : Confirm **recent maternal rubella** infection by **ELISA**

IgM

Rising titer of IgG in 2 samples

2<sup>nd</sup> : Confirm **fetal affection** by **DIF** : Detect **Ag in amniotic fluid**

→ **+ve results in 1<sup>st</sup> trimester** → therapeutic **abortion**



B-After birth

Live newborn : by **ELISA**

Detection of antirubella IgM  
in serum

Still birth : **virus detection** from organs

Culture on MKTC

Rubella virus *interferes* with CPE of **Coxsackie** or **ECHO**

DIF

Detection of viral Ag

## Prevention & Control

Vaccinate women in

School age

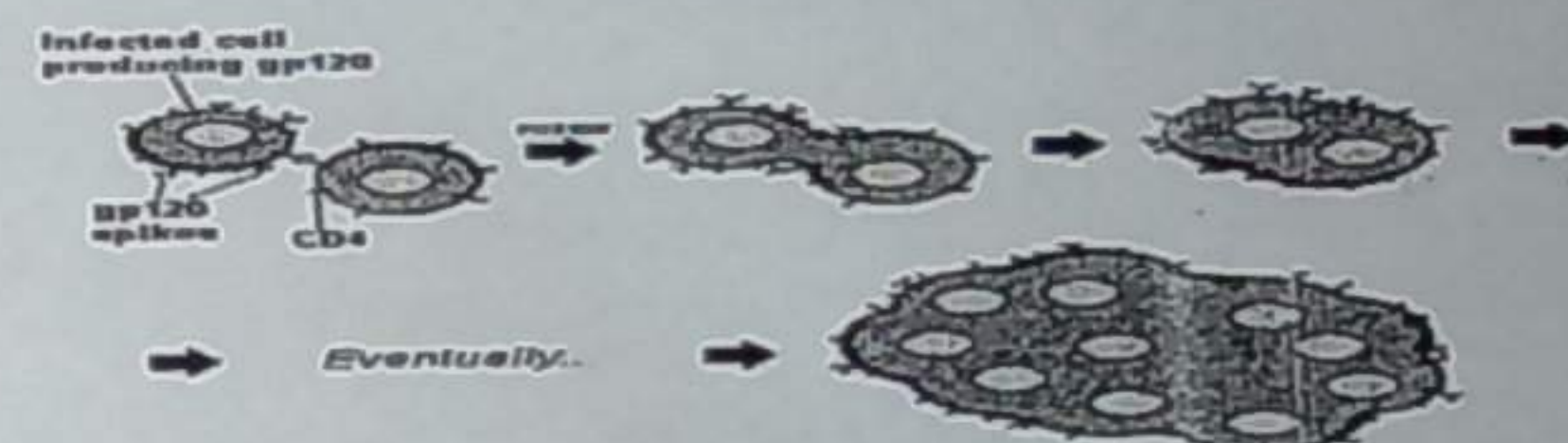

Childbearing age. Avoid pregnancy for 3 ms

Therapeutic abortion in 1<sup>st</sup> trimester

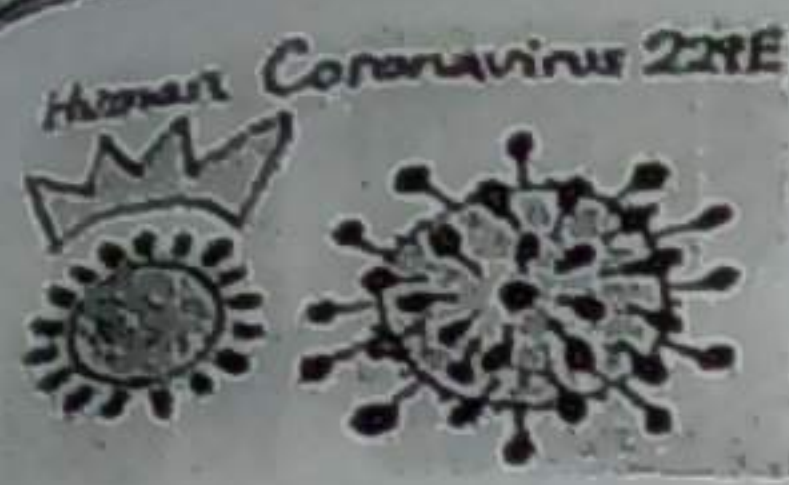
If **recent** maternal infection & fetal affection are **confirmed**



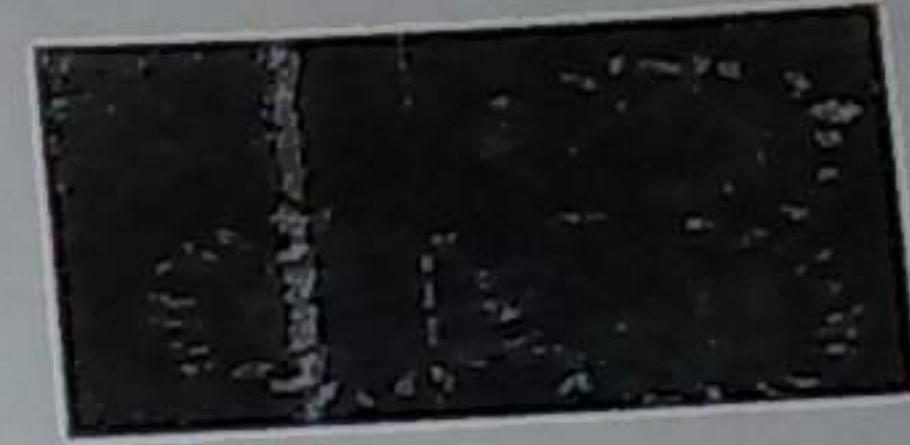
# Laboratory diagnosis of Myxoviruses

	Influenza V	HPIV	Measles	Mumps	RSV
I-Specimen	N a s a l   a s p i r a t e			Saliva , CSF, urine	Nasoph.aspirate
II-Direct detect.					
A-DIF	D e t e c t s                      v i r a l                      A g				
B-RT-PCR	D e t e c t s                      v i r a l                      R N A				
III-Isolation					
A-Culture	Monkey kidney tissue culture				Hela cells
B-Recognition of growth	♦Haemadsorption				NO
	NO	♦CPE → giant cell. 			
		♦Intranuclear & Intracytoplasmic IB 	NO	+ Syncytia	
C-Serotyping by HIT	Add specific <i>monoclonal Ab</i> to identify <i>serotype</i>	NO			
IV-Serology	ELISA 1-IgM2-Rising titer of IgG 4 folds in 2 samples ( most important)				ELISA 10





# Corona Viruses



## Structure

**Genome**: SS RNA+ve sense, **largest RNA genome**  
**Capsid**: Helical  
**Envelope**: Has club-shaped projections → crown or solar corona-like

## Mode of transmission

Inhalation of droplet aerosols      Close contact: touching or shaking hands      Feco-oral

## Clinical picture

Respiratory diseases				Enteric diseases : enteritis in neonates
Common cold 2 <sup>nd</sup> most frequent cause after Rhino V	Bronchitis	SARS	MERS	Destroys epithelial cells (as Rota V.) Loss of absorptive capacity of enterocytes

	SARS(Severe acute respiratory syndrome)	MERS (middle east resp.synd.)
1-Virus	SARS CoV (mutant corona)	MERS CoV (new corona)
2-NR		Bats
3-Origin	China 2002	Saudia Arabia 2012-2013
4-MOI	Airborne	Direct or indirect contact with camels in SA,Qatar&Egypt.
5-Receptor	Angiotensin converting enzyme-2 on respiratory epithelium → Dysregulation of fluid balance → Edema in alveolar space	CD26 on respiratory mucosa ( not ang.conv.enz.)
6-Pathog.	1-Cytokine storm in blood for 2ws. 2-Virus is detected in liver,kidney&SI 3-Leukopenia & thrombocytopenia	
7-Cl.P	1-Atypical pneumonia : (interstitial ground glass infiltrate in X rays) non productive cough, fever(38C),dyspnea&hypoxia 2-Acute respiratory distress → Acute respiratory failure (10%)	Fatal pneumonia (outbreak)
8-Treatment	a.No specific antiviral tt.      b.Support vital organ functions in severe cases	
9-Prevention	a.Infection control precautions      b.No vaccine	

## Laboratory diagnosis

**Common cold**      **SARS & MERS**      **Diarrhea**  
 Clinical      1-Ab in serum      2-RT-PCR in resp.secretions      1-RT-PCR      2-EM

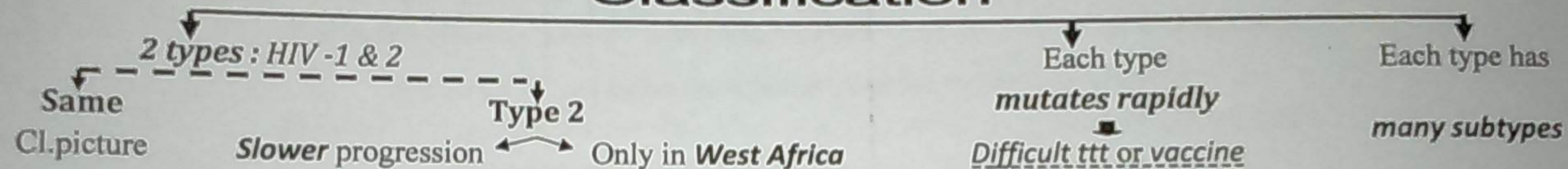


# Retroviruses

Characteristic feature (	Members of medical importance	
They have a <i>reverse transcriptase enzyme</i> that converts viral RNA into DNA (6) → <u>Integration</u> into host DNA → <u>Lifelong infection</u>	HIV • Slow • Cidal • Non oncogenic	HTLV 1 Oncogenic

## Human Immunodeficiency Virus (HIV)

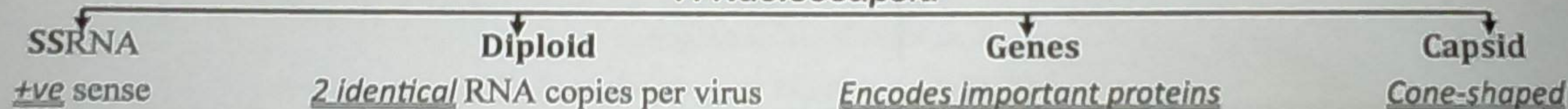
### Classification



### Structure (7)

#### I - Internal structures

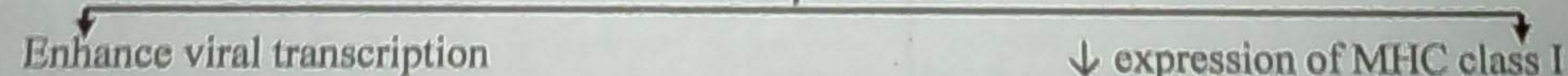
##### A-Nucleocapsid



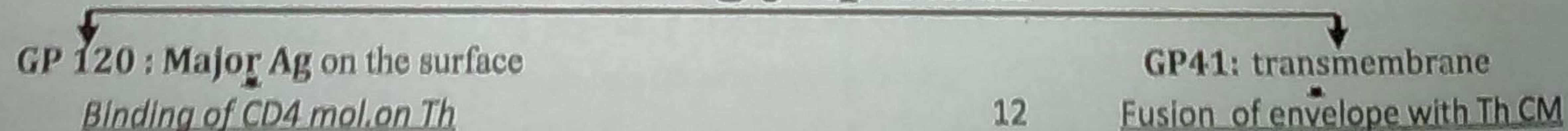
##### B-Internal proteins

A- 3 enzymes → Integration & Replication of virus			B- Structural protein
<b>Protease</b> Cleaves viral precursor proteins into <u>functional proteins</u>	<b>Reverse transcriptase</b> Converts SS RNA into <u>DS DNA</u>	<b>Integrase</b> <u>Inserts DS</u> DNA (provirus) into host chromosome	<b>P24</b> : Most abundant core protein Detected during early infection <u>Indicates viral replication</u>

##### C- Other proteins



#### II - Surface glycoproteins





# Retroviruses

Characteristic feature (	Members of medical importance	
They have a <b>reverse transcriptase enzyme</b> that converts viral RNA into DNA (6) → <u>Integration</u> into host DNA → <u>Lifelong</u> infection	HIV • Slow • Cidal • Non oncogenic	HTLV 1 Oncogenic

## Human Immunodeficiency Virus (HIV)

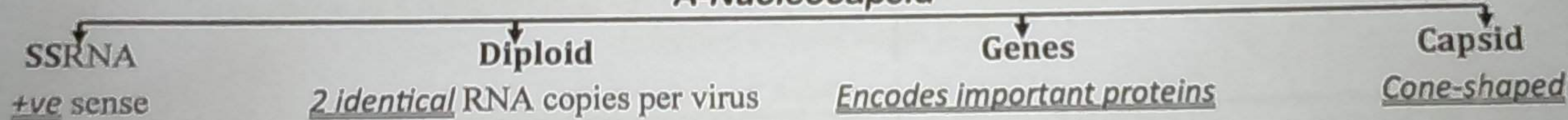
### Classification



### Structure (7)

#### I - Internal structures

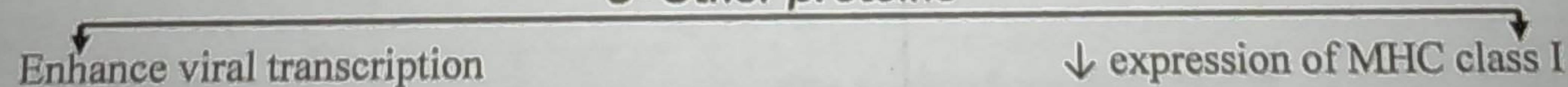
##### A-Nucleocapsid



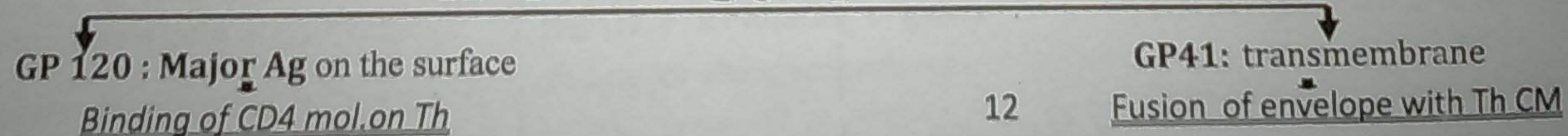
##### B-Internal proteins

A- 3 enzymes → Integration & Replication of virus			B- Structural protein
<b>Protease</b>	<b>Reverse transcriptase</b>	<b>Integrase</b>	<b>P24 : Most abundant</b> core protein
Cleaves viral precursor proteins into <u>functional proteins</u>	Converts SS RNA into <u>DS DNA</u>	<u>Inserts DS</u> DNA (provirus) into host chromosome	Detected during early infection <u>Indicates viral replication</u>

##### C- Other proteins



#### II - Surface glycoproteins





# Pathogenesis of HIV

## I-Tropism

CD4 + Th cells are the 1<sup>ry</sup> target of HIV

Certain subsets of monocytes express CD4 mol

## II-Attachment & Entry into CD4+ cells (8)

GP120 binds to CD4 mol. on target cell

Binds to coreceptor (chemokine receptor) :

CXCR4 on Th or CCR5 on MQ

Mutation of genes encoding for chemokine receptors

→ protection from inf. with HIV

GP41 fuses viral envelope with target CM Entry of virus contents & infection

## C-Replication in CD4+ cells & Release (9)

Reverse transcriptase converts RNA into DNA which is transported to nucleus

Integrase inserts DS DNA (provirus) into chromosome

Host cell polymerase transcribes viral gene into viral mRNA

Translation into viral proteins & replication of viral genome

Processing of capsid proteins by viral protease & Viral assembly & release by budding

Infection of new target cells

## D-Fate of infected cells

Killing of CD4 Th infected cells	Reversion of Th to a resting memory state	Monocytes
<p><b>1-Direct killing :</b> Large amounts of viruses are produced &amp; <u>buds off from cell surface</u></p> <p><b>2-Apoptosis :</b> Distortion of cell regulation by accumulation of viral proteins &amp; NA</p> <p><b>3-CTLs</b></p>	<p>A fraction of infected CD4 Th cells <u>survives</u></p> <p>Long term stable reservoir of virus</p>	<p>Are relatively <u>refractory</u> to CPE of HIV</p> <p>Survive &amp; harbor large quantities of virus</p> <p>i. Disseminate the virus to lung &amp; brain</p> <p>ii. Continue to produce virus for long period</p>

## E-Mechanisms IR evasion by HIV

1-Integration of viral DNA in host cells

persistent infection.

2-High rate of mutation in genes coding for env. glycoproteins

3-Down regulation of MHC class I required for CTLs to recognize infected cells



# Treatment

## I-Immunotherapy

Mc Ab against GP 120

Soluble CD4 mol.

## II - Antiretroviral drugs

### A-Aim

Suppress *HIV replication*, but *don't eradicate* the virus (no cure)

Protection of IS

### B-Modes of action

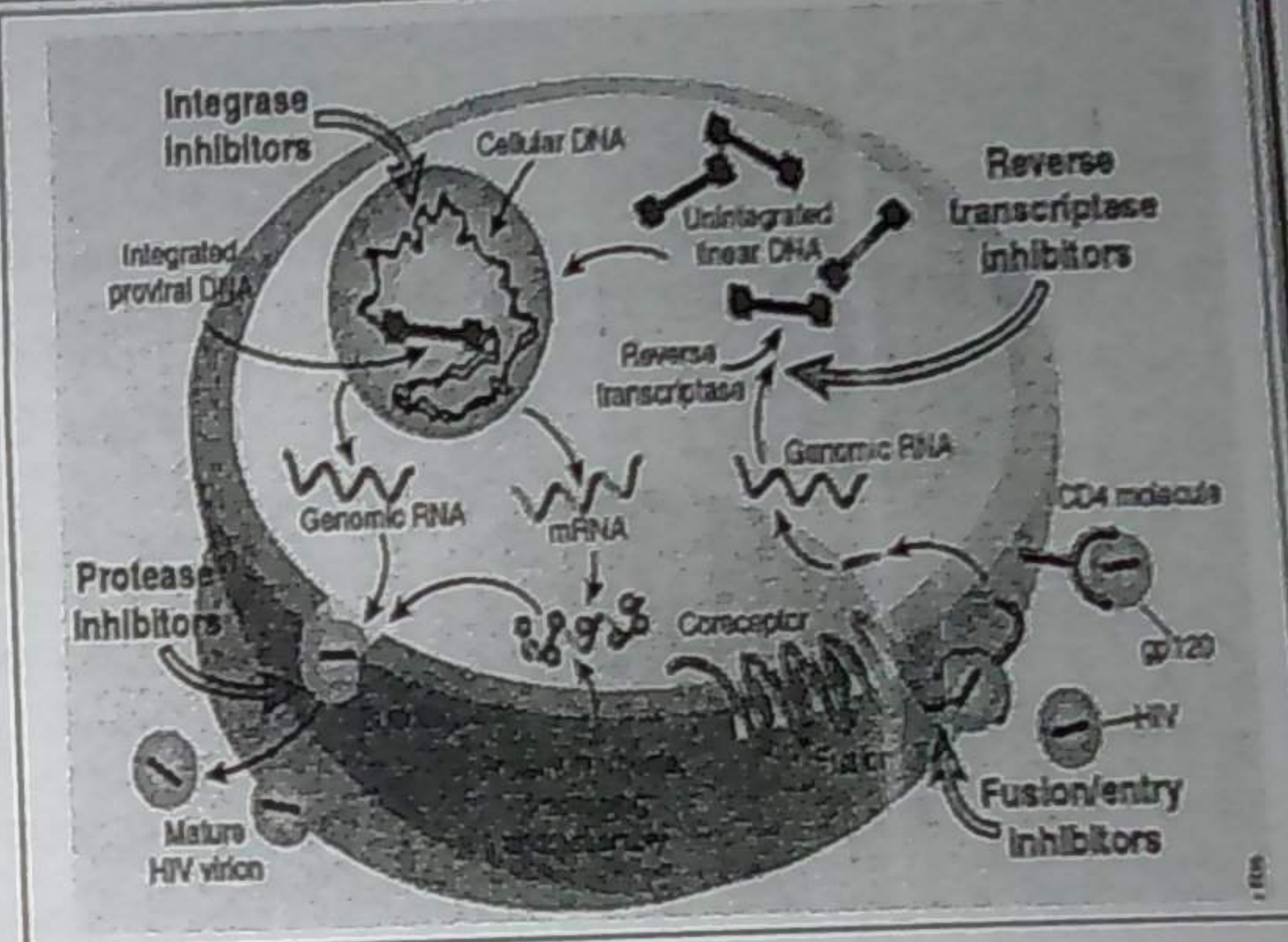
⊖ Fusion  
to lymphocytes  
Enfuvertide

⊖ RT  
Nucleoside analogues  
♦ Azidothymidine (AZT)  
♦ Dideoxyinosine (DDI)

Non nucleoside  
analogues  
Nevirapine

⊖ Integrase  
Raltegravir

⊖ Protease  
⊖ assembly &  
budding  
Indinavir



### C - Combination HAART (Highly active antiretroviral ttt) regimen

2 nucleoside analogues + Protease ⊖

Avoid development of resistance due to *high mutation rate* of HIV

### D-Monitoring of ttt : By measurement of

Virus load

CD4+ cells

## III - Antibiotics : for opportunistic infections

### Disinfection & Inactivation

10% Na hypochlorite & 70% ethanol  
on contaminated surface for 10 min

Heating at 56C  
Inactivates the virus in liquid

Exposure to undiluted bleach for 30 sec  
If the virus is present in clotted or unclotted  
blood in a needle or syringe



# Clinical picture : 3 stages (10)

	Early acute : 2-4 ws after infection	Middle latent	Late
A-Virological features	<p>1-Early</p> <p>a. <b>High viremia:</b></p> <p>i. Spread to many regions including <u>lymphoid tissues &amp; brain</u></p> <p>ii. Most infectious stage</p> <p>2- Later on</p> <p>a- <b>Low level viremia</b></p> <p>b. <b>Virus reaches set point</b></p> <p>Represents the amount of virus produced &amp; remains constant for yrs (differ between pts)</p> <p>→ <u>The higher the set point, the more likely the progression to symptomatic AIDS</u></p>	<p>HIV continues to replicate in lymphoid organs</p> <p>Large amount of virus is produced by LN cells &amp; remains sequestered in LNs</p>	<p>Collapse of LN architecture</p> <p>Loss of IS ability to trap HIV or other infectious pathogens</p> <p><b>Viral load ↑</b> in peripheral circulation</p>
B-Clinical features	<p>1- <b>Inf.mononucleosis like symptoms(90%)</b></p> <p>a. Fever, sore throat &amp; LN enlargement</p> <p>b. Maculopapular rash on trunk &amp; extremities</p> <p>2- <b>Asymptomatic (10% of cases)</b></p>	<p>• <b>Asymptomatic</b></p> <p>• Lasts 7-11 yrs</p>	<p>• <b>Long lasting fever (1m)</b></p> <p>• Weight loss • Fatigue</p> <p>• ↑ severity of opportunistic inf.</p>
C-Immunol. Features	<p>1-CD4 + count</p> <p>a. <b>Early</b> : ↓ significantly</p> <p>b. <b>Later</b> : <i>revert to normal by</i> : ↑ CD8+ cells &amp; Ab against HIV</p> <p>2- <b>Seroconversion</b> : Detection of Abs in serum</p> <p>♦ Usually 1-4 ws after infection</p> <p>♦ <b>May be delayed up to 6 ms : Window period</b></p> <p>No Abs are detected although the viral load is high</p>	<p><b>Early : Immune competence</b></p> <p>Generation of <i>new</i> CD4+T cells <u>compensates destroyed ones</u></p> <p><b>Immune surveillance</b> prevents most of infections</p>	<p>♦ <b>CD4 + count</b> ↓ to &lt; 200 cells/ mm<sup>3</sup> (The lower normal limit is 500 cells/ mm<sup>3</sup>)</p> <p>♦ The 2 characteristic manifestations of AIDS are <b>Pneumocystis carinii</b> &amp; <b>Kaposi sarcoma</b></p> <p>♦ <b>Other opportunistic inf.</b></p> <p>a. <u>Bacterial</u> : Listeria M.TB, M.avium intracellulare</p> <p>b. <u>Viral</u> : CMV, HSV &amp; VZV.</p> <p>c. <u>Fungal</u> : Candida, Cryptococcus</p>



In neonates, viral RNA  $\uparrow$  rapidly in 1<sup>st</sup> few ms of life & **doesn't**  $\downarrow$  rapidly as in adults as the IS is immature

## **Pediatric AIDS**

The level of RNA predicts the  
rapidity of progression to AIDS

Signs of AIDS can appear  
early by 5 ms (80% of cases)

### **Laboratory diagnosis**

**A-An initial HIV screening test** : either by

**1-Ab tests** : Detection of Abs for both HIV 1&HIV 2 Ags.

**2-Ag/Ab test** : detection of Abs & P24 Ag

**B-Follow up testing** : performed if the initial result is +ve

**1-Ab differentiation tests** : distinguishes HIV1 from HIV2 tests

**2-Qualitative & Quantitative detection of HIV nucleic acid:**

Performed if the initial HIV screening tests are +ve

a. Detects initial baseline viral load (set point)  $\rightarrow$  Predicts time of AIDS onset  
(  $\uparrow$  set point  $\rightarrow$  faster AIDS onset )

b. Prognostic marker after initiation of ttt.

### **C-CD4 cell count**

(The lower limit of normal CD4 count is 500 cells/mm<sup>3</sup>)

$\uparrow$  opportunistic inf. when CD4 count *falls* < 200 cells/mm<sup>3</sup>



Determines whether a pt needs chemoprophylaxis against opportunistic inf.:

### **Diagnosis of HIV inf. in newborns & infants**

**RT-PCR** : detects viral RNA

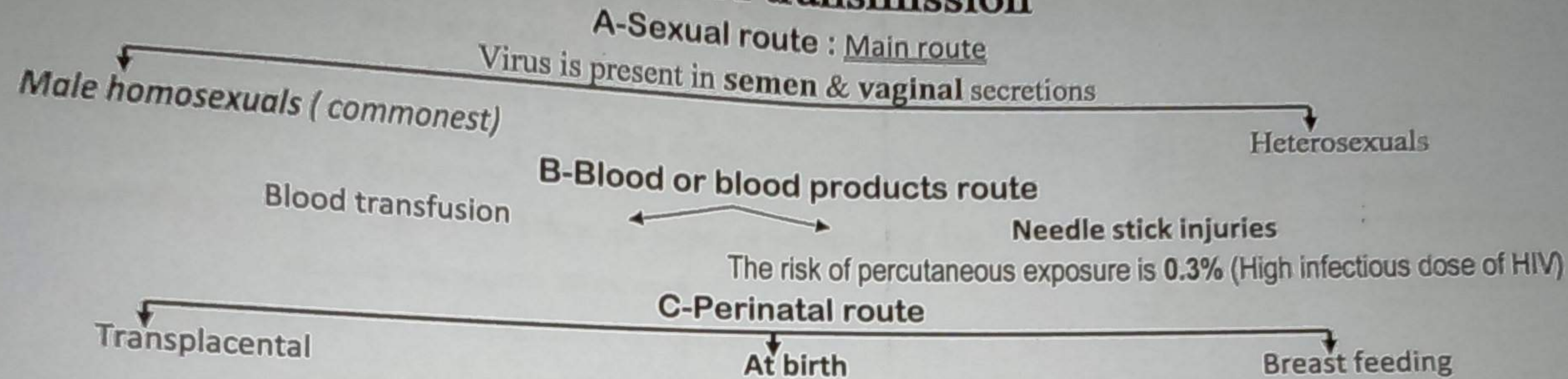
❖ *Ab detection isn't useful*

Transferred maternal Abs are present up to 18 ms

whether the newborn is infected or not



## Modes of transmission



## Prevention & Control

### General Measures

As HBV (E)

Vaccine : under trials & is hindered by

Rapid *mutation*  
in *Env* region

No viral *exposure* to *Abs*  
(Spread by fusion)

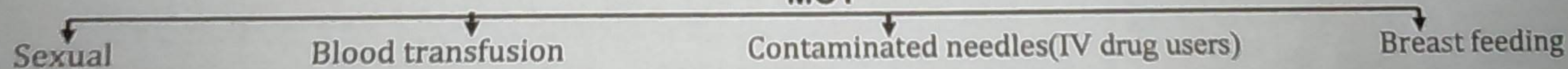
No animal models  
for AIDS

Post exposure prophylaxis after needle stick injury from HIV positive pts

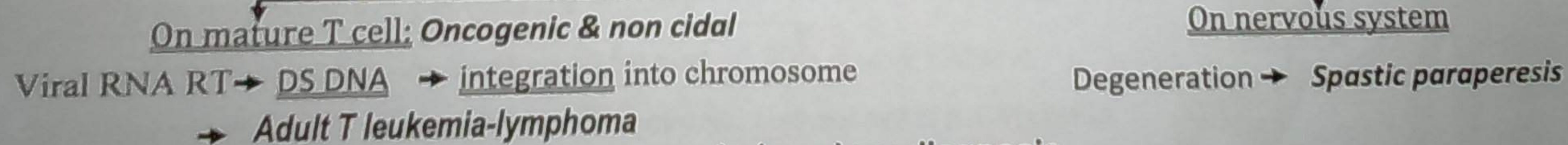
Risk of getting HIV	Drugs	Follow up by HIV testing
Very low ( $< 1$ in 100 exposures)	Anti HIV drugs within 72 hrs $\rightarrow$ 28 days $\downarrow$ replication of HIV & its spread	At 6ws, 3ms & 6ms

## Human T cell lymphotropic virus 1 (HTLV-1)

### MOT



### Pathogenesis & Ds production



### Laboratory diagnosis

RT-PCR: Detects viral RNA

ELISA : Detects Abs



# Rhabdo Viruses : Rabies virus

## Structure

### A-Nucleocapsid

ss RNA : -ve sense

Helical

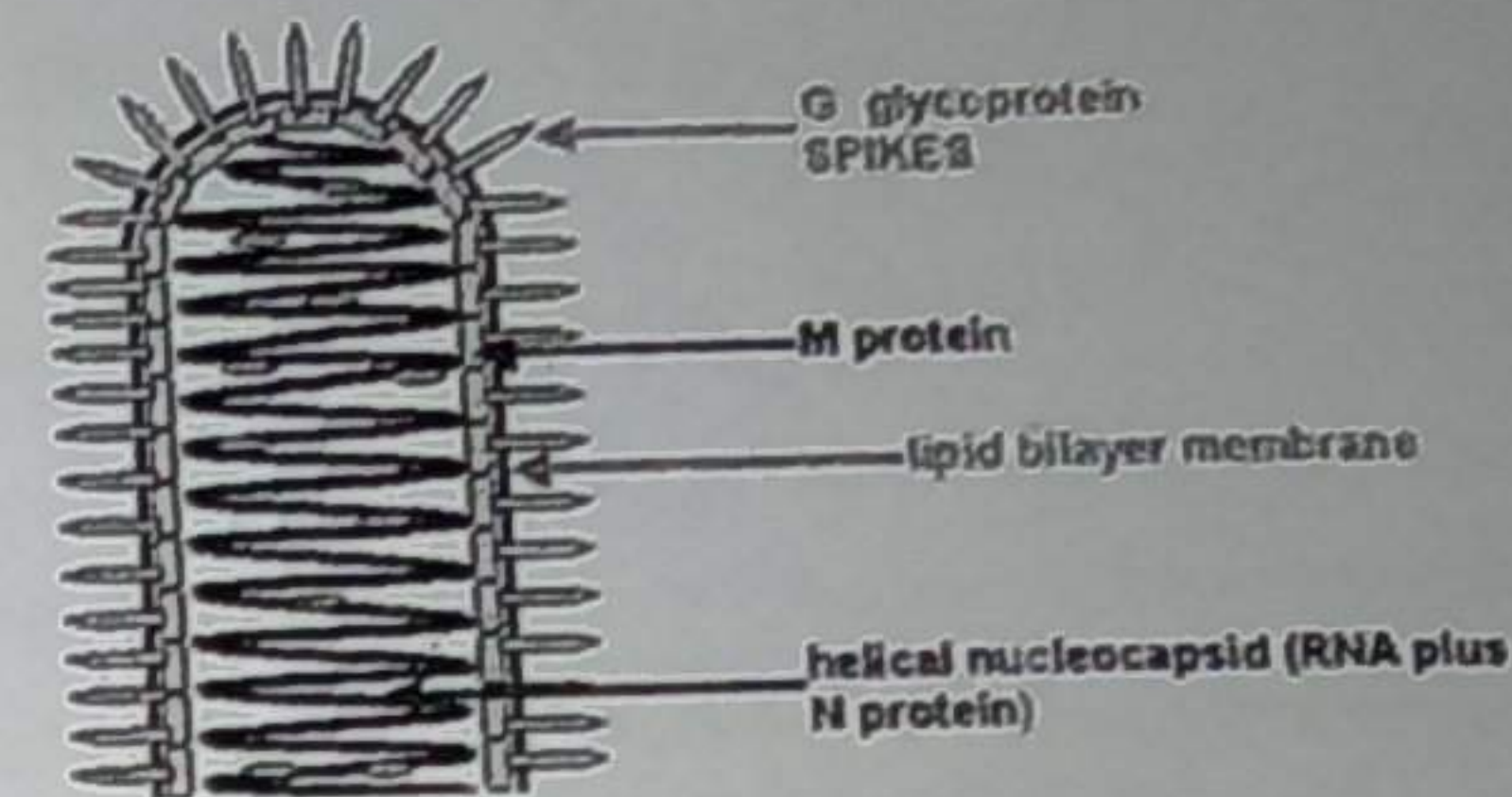
Bullet shape

### B-Envelope

Has glycoprotein projections → viral entry → target of neutralizing Abs

## Host range : Broad

Infects all mammals → Lethal acute encephalitis



## Modes of transmission & Animal reservoirs

### 1-Bite of rabid animals : virus in saliva of

Dogs ,cats & wolfs : main reservoirs

Aggressive behavior due to encephalitis



Bats

Healthy



2-Corneal transplantation (very rare) : from infected *cadaver*

3-Airborne aerosols in : bat caves & laboratory work

## Pathogenesis

1-Virus multiplies in striated muscles at site of bite

Invades sensory neurons

↓ Retrograde axonal transport

Reaches spinal cord & brain → multiplication

Encephalitis

Neuronal death

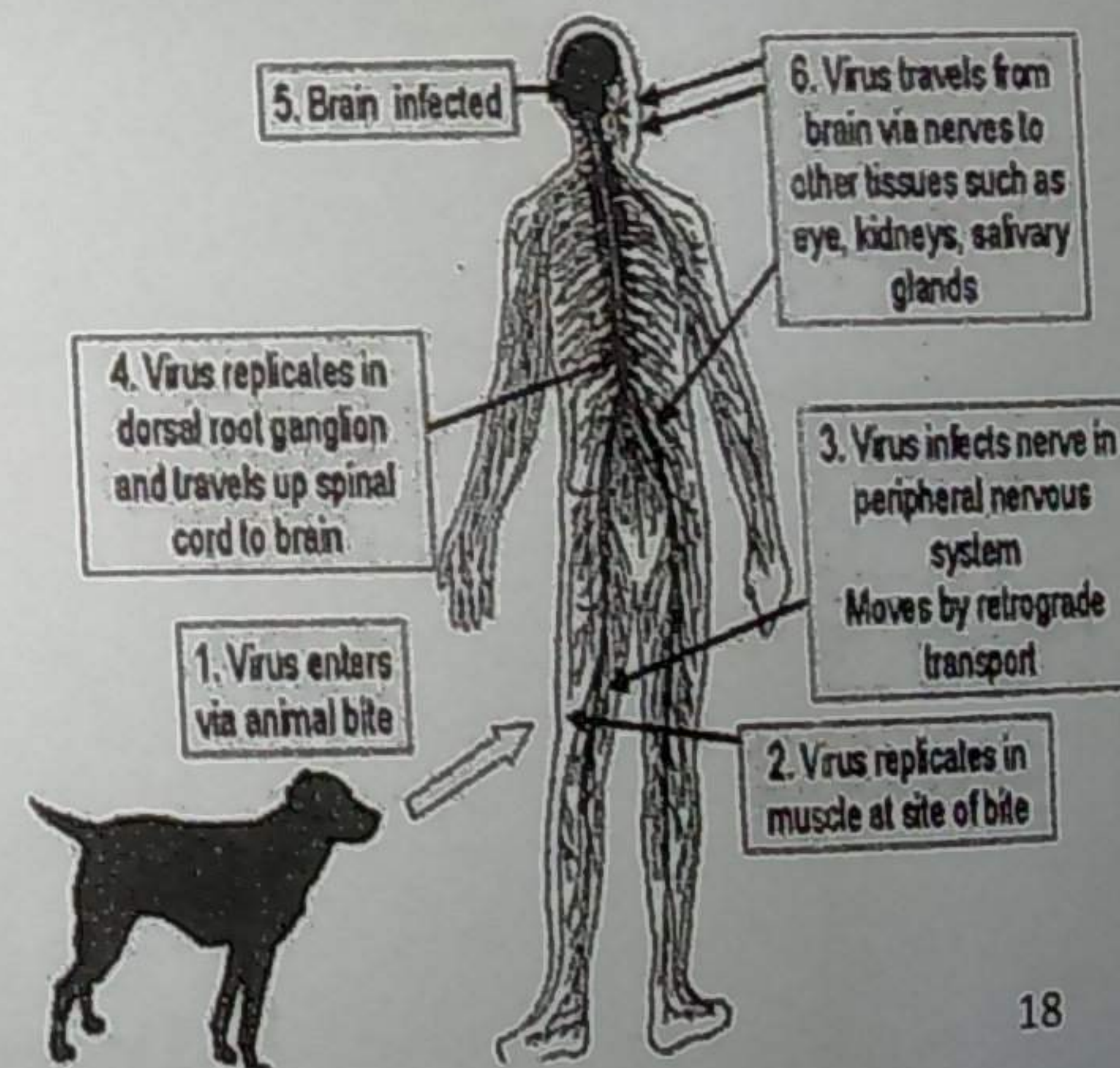
IC Negri bodies

2-Virus migrates via peripheral nerves

Salivary glands → saliva → transmitted by bite → Eye, skin & Kidneys

3- Viral replication is restricted to neuronal tissues with no viremia

Virus is protected from IS → No or little IR





A-IP : 4-12 WS

Longer with bites in limbs

**1-Prodrome of non specific symptoms** : Fever ,anorexia & change in sensation at the site of bite

**Furious rabies : 80% of cases**

Brain is involved

- Excitement, seizures

- **Hydrophobia** : fear to swallow due to painful spasms of swallowing muscles

Spinal cord is 1rly involved

♠ Ascending paralysis & respiratory failure

## Rules

Several tests are necessary for antemortum diagnosis  
(no single test is sufficient )

Saliva, spinal fluid & Skin biopsies of hair follicles at the nape of neck

**DIF: Viral Ag**

### RT-PCR: Viral RNA

## Saliva, CSF or urine

### Intracerebral inoculation in mice

## On human diploid cell culture

↓ Encephalitis

Examine brain for Ag & Negri bodies

Serum & CSF **Abs** appear **late** during ds progression

Detection of Negri bodies in brain or spinal cord by L/M



## Management of rabies

### General rules

Immediate washing of wound  
with soap & H<sub>2</sub>O

Early post exposure prophylaxis

• Vaccine •  $\pm$  Igs

Tetanus  
immunization

No wound suturing  
before local Ig infiltration

### Post exposure prophylaxis

**A-Unvaccinated or vaccinated from > 5 yrs or Incomplete vaccination**

RIG + vaccine for both bite & non bite exposure (regardless of time interval between exposure & initiation of PEP)

Rabies Igs (RIG): Human or equine

1 dose IM on day 0 & up to day 7

Most into & around wound

Rest in gluteals

Rabies vaccine

5 doses: 1 ml IM Days :0, 3, 7, 14 & 28

### Important rules

**Discontinue PEP** if the animal was captured &  
proved to be *non rabid* by DIF

Any one coming *into contact* with CSF,, saliva or MM  
of *suspected person* should receive *complete prophylaxis*

**B-Completed the schedule of vaccine within last 5 yrs**

2 doses (1ml) of vaccine IM : days 0&3

### Rabies vaccines

Human vaccines : *Inactivated cell derived vaccines*

Human diploid cell V. (HDCV): *Gold standard*

Rhesus monkey vaccine

Duck embryo vaccine: Low immunogenecity

### Preexposure vaccination

**A-Doses** : 3 doses: day 0, 7, 21 or 28

**B-Indications** : few people

High risk individuals	Traveler's to countries where rabies is widespread if	
<ul style="list-style-type: none"> <li>• Veterinary doctors &amp; laboratory workers</li> <li>• Animal handlers</li> </ul>	visiting remote villages where <u>medical care is difficult to obtain</u>	<u>staying &gt; 1 m</u> in area where rabies is common

### Prevention & control

#### A-Animals

Eliminate stray animals

Vaccination of domestic dogs & cats

Avoidance of wild animals

**B-Follow preexposue & postexposure prophylaxis**



# Arboviruses

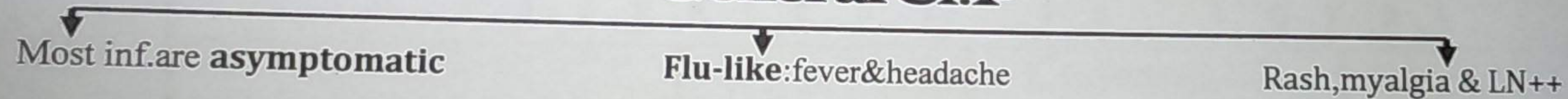
(Arthropod-borne viruses)

## Structure & Classification

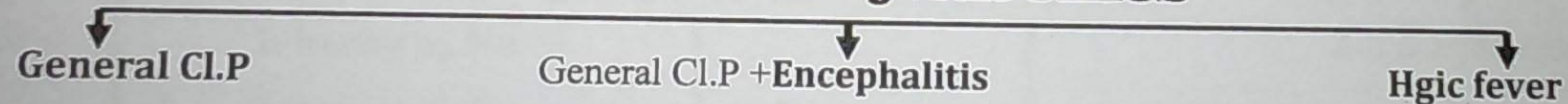
100 V infect human

	Flavi V	Toga V	Bunya V
1-Genome	SS RNA + ve sense		SS RNA -ve sense & segmented
2-Envelope	E n v e l o p e d		
3-Members	<i>i. Dengue</i> Fever V. <i>ii. West Nile</i> fever V. <i>iii. Yellow</i> fever V.	<i>Sindbis</i> V.	<i>i. Sandfly</i> fever V. <i>ii. Riftvalley</i> fever V.

### General Cl.P

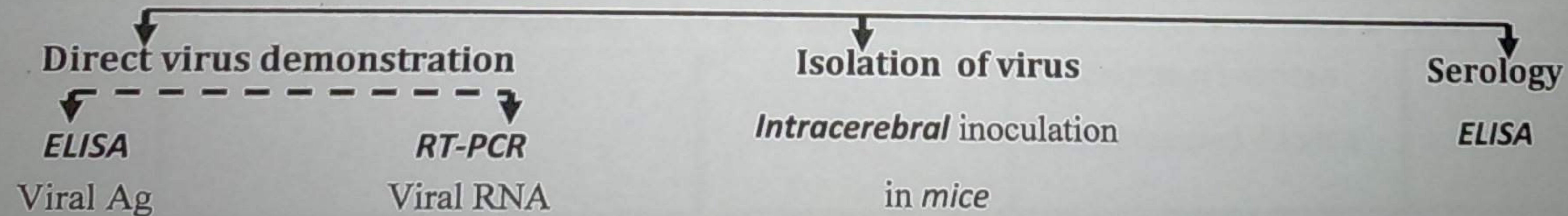


### Clinical syndromes



### Laboratory diagnosis

Specimen : blood





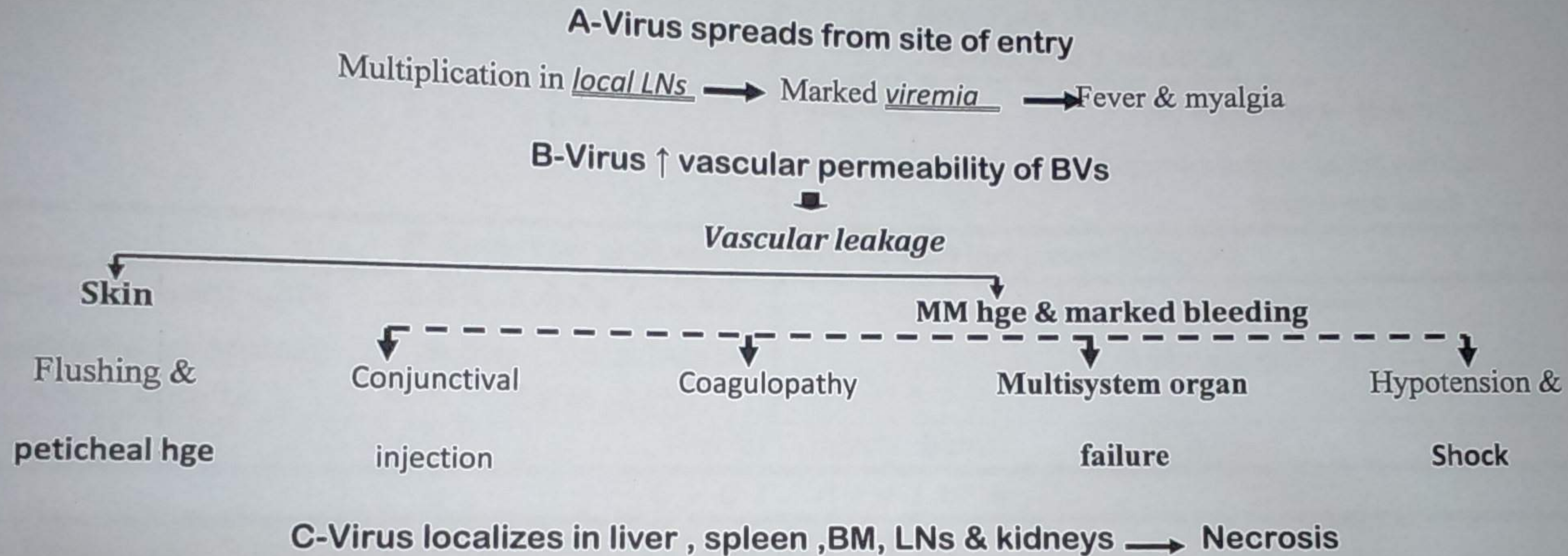
# Arboviruses causing Fever & Encephalitis

	Arboviruses ds with fever		Arboviruses ds with encephalitis	
	Sandfly Fever	Sindbis Fever	Rift Valley Fever	West Nile Fever
A-Structure & Classif.	Bunya V.	Toga V.	Bunya V.	Flavi V.
B-Reservoir	<p>Human</p> <p>Vect.: Phelobotomus papatsii</p> <p>Human</p>	<p>Bird</p> <p>Vector: Culex</p> <p>Bird</p>	<p>Animal: cattle, sheep</p> <p>Vector: Culex</p> <p>Animal</p>	<p>Bird: crows &amp; migrat. birds</p> <p>Vector: culex</p> <p>Bird</p>
C-MOT	V e c t o r i n f e c t s h u m a n			
			Animal infects human by blood & its products	
	P r e v a l e n t i n E g y p t			
			1 <sup>st</sup> outbreak in 1977	
D-CI.P	1 - G e n e r a l C I . P			
	2-Neck rigidity & conjunctivitis		2- Encephalitis	
			3-Retinitis → blindness 4-Hgic fever (rare)	
E-Prevention	1 - Vector control	2 - ↓ exposure to vector : Protective clothes & insect repellants		
			2-Animal vaccines Live attenuated & killed	



# Viral Hemorrhagic Fever

## Pathogenesis & Complications



## Classification

Flaviviruses		Bunyaviruses		Arenaviruses	Filoviruses
Yellow fever	Dengue Fever	Rift Valley F	Hantavirus ds	Lassa Fever V	Ebola&Marburg ds
<i>Arbovirus-associated</i> Hgic fevers			<i>Rodent-born</i> Hgic fevers		<i>African</i> Hgic fevers



I - Arbovirus-associated Hgic fevers	
Yellow fever	Dengue fever
A - Structure & Family : <i>Flavivirus</i>	
	4 serotypes : Den 1,2,3 &4 Infection with 1 serotype Life long immunity to it      No immunity to others Repeated infections are common in endemic areas
B-Reservoir & Mode of transmission (not present in Egypt)	
1-Jungle (Sylvan) cycle Monkey-Vector-Monkey Aedes africanus	2-Urban cycle : in towns Human - Vector-Human Aedes aegypti
Vector infects human	
C - C I . P i c t u r e	
1-General Cl.P (E)	
Classical Dengue fever	
2-Severe disease	
Dengue hgic F (immunological compl.) & Dengue shock syndrome	
a.Hgic manifestations	
Black vomitus	Skin Hge : Purpura,thrombocytopenia &shock
b.Jaundice &Renal failure	
D - P r e v e n t i o n	
1 & 2 : as before	
3-17 D vaccine : <u>Live attenuated</u> 1dose SC given to travelers and residents of endemic areas Immunity for 10 yrs	



II-Rodent-born Hgic fevers			III-African (non-rodent) Hgic fevers
Lassa fever Virus	Hanta V associated syndromes		Marburg & Ebola viruses
Arenaviruses		A-Family	
	Bunya viruses		Filoviruses
House rat		B-Reservoir	
	Field rat		Unknown, but may be bats
C-Modes of transmission			
Exposure to excreta of infected rats ( urine, feces)		• Marburg: Exposure to African green monkeys • Ebola: Direct contact with pt blood or secretions	
♦ Direct contact & contam. food ♦ Human to human contact	Inhalation of aerosols of rodents excreta (No human to human trans.)		
D-Clinical Picture			
1- Most inf. are asymptomatic 2-Multisystem ds: Liver, spleen & kidneys	1-Hgic fever & renal syndrome 2-Pulmonary syndrome	Both cause same ds 1-Fever, vomiting & diarrhea 2-Bleeding into GIT 3-Hepatic affection 4-DIC & shock	
E-Prevention			
Rodent control (difficult to eliminate)		1-Follow infection control precautions 2-No vaccines	
F- Lab. diagnosis of Ebola & Marburg			
1-RT-PCR: detection of viral nucleic acids    2-Serology : Rising Ab titer. 3-Virus isolation (extreme care during handling specimen)			
G-Treatment of Ebola & Marburg			
1-Igs against the virus : has variable results. 2-No antiviral drugs			

25



# **virology 3**

Non enveloped RNA Viruses      Prions

Oncogenic Viruses      Collections



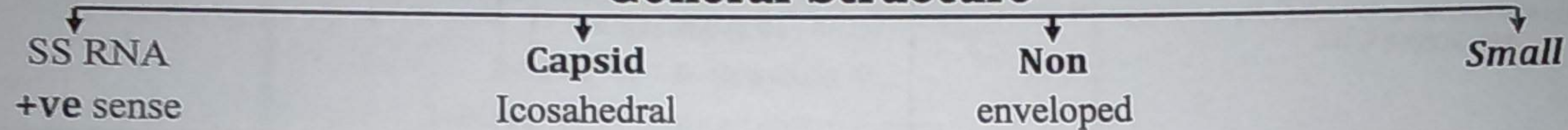
# Non enveloped RNA

Picorna Viruses

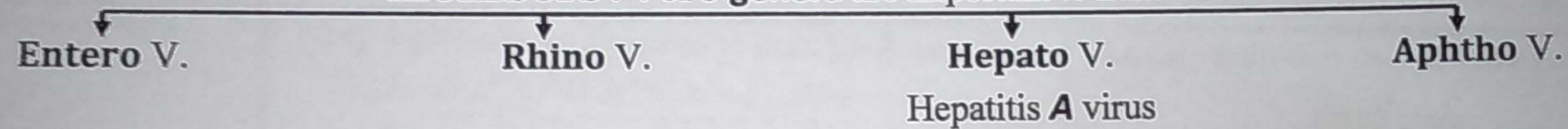
Reoviruses (Rota viruses)

## Picorna Viruses

### General Structure



**Members** : 4 of 9 genera are important to humans



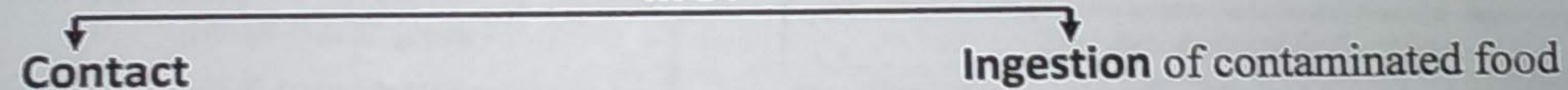
## Aphthovirus of cattle

SOI : Zoonotic

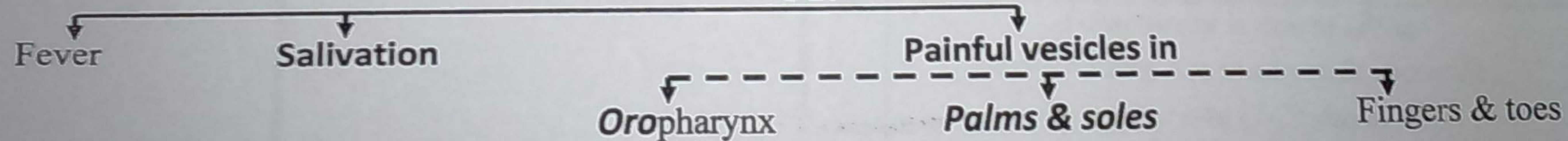
Causes **Foot & mouth ds** in cloven-footed animals e.g cattle



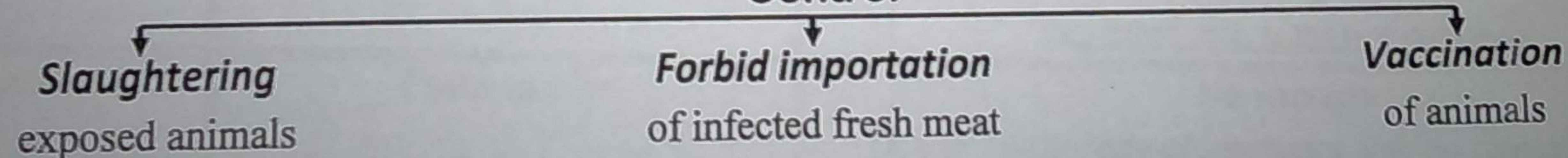
### MOI



### CL.P



### Control





## Comparison between Enteroviruses & Rhinoviruses

	Enteroviruses	Rhinoviruses
A-Structure	As before	
B-General characters	1 -Acid <b>stable</b> & OT:37 C 2-Inhabit <b>GIT</b>	1-Acid <b>labile</b> & OT :33 C 2-Inhabit <b>nose</b>
C-Classification	<b>4 members :</b> 1-Polio V. 2- Coxsackie V. 3-ECHO V. 4-Other enteroviruses	<b>100 serotypes</b>
D-MOI	1-Feco-oral ( main) 2-Droplet	1-Droplet (main) 2-Direct contact
E-Pathogenesis	1ry replication in <b>oropharyngeal LN &amp; tonsils</b> Replication in GIT & Peyer's patches ↓ Shed into feces ↓ Viremia ↓ into feces      Spread to target organs → Symptoms	<b>Local</b> replication only in <b>nasal mucosa</b> <b>No viremia</b> ↓ Congestion & desquamation of epithelial cells ↓ ↑ nasal secretions
F-Disease production	1-Asymptomatic ( most cases) 2-Fever & rash in children	<b>Common cold</b> ( most common cause)
G-Complications	<b>Meningitis</b> (rare) Mild encephalitis	<b>2ry bacterial infection</b> Sinusitis & OM      Bronchitis
H-Immunity		1-Recovery is due to <b>IFNα</b> 2-Neutralizing Abs in serum & secretions appear late (7-21 days) 3-Local <b>IgA</b> & serum <b>Abs</b> are <b>short lived</b> ↓ <u>Repeated infections are common</u>
I-Prevention	<b>Polio vaccine</b>	<b>No vaccine</b> Due to <b>multiplicity of serotypes</b> with no cross protection



# Polio Viruses

**Structure :** as before

**Serotypes & Immunity :** 3 serotypes

Life long immunity to infecting serotype

No cross protection

## Clinical picture

**A-Asymptomatic polio :** most cases

If the virus replicates *only in GIT*

**B-Abortive polio :** only in 5 % of infections

Most common  
symptomatic  
form

Viremia

Fever, abdominal pain  
& constipation

Neutralizing Abs develop

Recovery

Rarely

Progression  
to NS

**C-Non Paralytic polio (aseptic meningitis) :** 1-2 % of infections

Above symptoms + Neck stiffness & pain

Complete recovery

**D-Paralytic polio :** < 1% of infections

Virus spreads  
from blood  
to AHCs  
Multiplication

Pred.F.

Tonsillectomy in child  
with inapparent inf.  
V.in nasopharynx enters  
*cut nerve fibers*

Mild lesion

Nerve cells  
recover

Destruction

of nerve cells  
Flaccid  
paralysis

Muscle atrophy

Due to nerve supply affection  
(muscle itself isn't  
affected)

## Reaction to physical & chemical agents

Poliovirus is inactivated by

Heating at 55C for 30 min,  
but Mg prevents this inactivation

Chlorine : 0.1ppm  
for drinking water



## Prevention & Control

### I - Active immunization

Oral polio vaccine (OPV) : Sabin	Inactivated polio vaccine (IPV) : Salk
<b>A-Contents &amp; Preparation</b>	
3 serotypes grown on MKTC → 3 doses given at 2, 4 & 6 ms	
<b>B-Effects</b>	
Induce <b>systemic Abs</b> : IgG&IgM → <u>neutralization</u> of virus → <u>Protection</u> of CNS from <u>wild</u> virus (100%)	
<b>C- Advantages : Live attenuated</b>	<b>C-Disadvantages : Killed ( by formalin )</b>
<b>1-Booster</b> dose at 4-6 yrs	<b>1-Repeated booster</b> doses
<b>2-Oral</b> → Multiplication in intestine → <b>slgA</b> → GIT protection	<b>2-IM</b> → No .....
<b>3-Production of herd immunity</b> Attenuated virus passes in stools of vaccinated children Infects <b>non vaccinated</b> children	<b>3-NO</b>
<b>D-Disadvantages : Live attenuated</b>	<b>D- Advantages : Killed</b>
<b>1-Contraindicated in immunodeficient individual</b>	<b>1-Mainly used in immunodeficient individual</b>
<b>2-Interference</b> Its <u>replication &amp; immunity</u> is interfered if <b>another entero V.</b> is <b>infecting</b> the <b>gut</b> of the child <u>Not given</u> to a <u>feverish</u> child	<b>2 - No interference</b>
<b>3-Must be stabilized by MgCl<sub>2</sub></b> <u>Prolongs</u> its potency at <u>4 C</u> (for 1yr) & <u>25C</u> (for ws)	<b>3-Stable</b>

### II-Passive immunization

Igs given shortly before infection to asymptomatic contacts → **Prevent paralysis** for ws

### III-General measures

↓  
Proper sanitation
↓  
Avoid tonsillectomy in feverish children

**Treatment** : No antiviral ttt



# ECHO ( Enteric Cytopathic Human Orphan ) Viruses

Classification : 34 serotypes

## Diseases

Aseptic meningitis

Fever : with or without rash



## Coxsackie Viruses

Classification : according to effect on mouse

Group A : 23 serotypes

Group B : 6 serotypes

## Diseases

1-Both group A & B : a. Aseptic meningitis b. Common cold

### 2-Group A

Herpangina : small children

Hand, foot & mouth ds

Hgic conjunctivitis

Pharyngitis

Vesicles: Palate & tongue

Pharyngeal ulcers

Vesicles: Palms & soles



### 3-Group B

Pleurodynia (epidemic myalgia)

Myocarditis : in neonates

Type I

Generalised ds : in infants

Unilateral severe  
pain in intercostals

Self  
limited

♦ Arrhythmia

High

♦ Heart failure

mortality

DM

♣ Heart & liver

♣ Brain



No antiviral drugs or vaccine



### Other enterovirus types

Type 68	Type 70	Type 71
✓ Pneumonia ✓ Bronchitis in children	➤ Acute hgc conjunctivitis	❖ Aseptic meningitis & encephalitis. ❖ Paralysis

### Laboratory diagnosis

	Polioviruses	Coxsaki viruses	ECHO Viruses
A-Specimen	1-Throat swab : early    2-Stools : late    3-CSF : in meningitis		
B-Direct demonstration of virus	RT-PCR : detects RNA ↓ Rapid diagnosis of <i>meningitis</i>		
C-Isolation of virus	On MKTC → CPE  ✓ Serotyping by Nt : addition of monoclonal Abs		
D-Serology: Nt	Rising titer of IgG 4 folds in 2 samples		
		Not reliable due to <i>multiplicity of Ags</i>	

### Viral gastroenteritis

DNA	RNA			
♦ Adenoviruses type 40&41	♦ Rota viruses ♦ Corona viruses	♦ ECHO viruses ♦ Coxsackie viruses	♦ Calici viruses e.g <u>Norwalk</u> virus	♦ Astroviruses





# Rota viruses

Family: REO (respiratory enteric orphan)



1-Genome	2-Capsid	Envelope	Serotypes
• <u>DS RNA</u> -ve sense • <u>Segmented</u>	*Double layered * <u>Wheel shape</u>	Non enveloped	5 serotypes cause human ds

Feco oral & contact with contaminated surfaces

## Mode of transmission

Nosocomial infection

## Pathogenesis

1<sup>st</sup> replication occurs in villi of small intestine

↓ reabsorption of glucose & Na<sup>+</sup>

Virus is excreted in large amounts in stools

for 2-12 days

Cl. P

Most common cause of infantile gastroenteritis  
(asymptomatic in adults)

Abdominal pain, vomiting & severe watery diarrhea

→ Dehydration → death

## Immunity

Local immunity (IFNα & IgA) is more important, but short lived

Reinfections are common

Maternal Abs protect infant in 1<sup>st</sup> ms  
SIgA Through Breast Milk protect the Baby  
in 1<sup>st</sup> ms

Treatment: Fluid & electrolyte replacement

## Prevention

Waste water sanitation	Live attenuated oral vaccine: Given in early infancy	
most important	<u>Pentavalent RV5 Human-bovine reassortants (3 doses)</u>	<u>Monovalent RV1 Human type (2 doses)</u>

*Handwritten notes:*  
Human Rotavirus  
Influenza virus  
Hepatitis virus

## Laboratory diagnosis

Direct detection: in stools

Serology: ELISA

EM	ELISA	RT-PCR	Serology
<u>Wheel shape</u>	<u>ELISA</u> <i>The most reliable</i> Detects viral <u>Ag</u>	Detects viral <u>RNA</u> (most sensitive) <u>Genotyping</u> the virus in stools	Rising Ab titer



# Oncogenic Viruses

Viruses that induce **host cell transformation**

*Induce host cell Transformation*

## I-Characters of transformed cells

*Malignant & mostly*

*Benign*

### Change in growth pattern

↑ growth rate

Loss of contact ⊖

### IC changes

↑ metabolic rate & glycolysis

Integration of viral NA into genome

### Surface changes

New virus specific Ags

### Tumorigenicity

Produce tumor in test animal

## II - Mechanisms of cell transformation

Tumor DNA & RNA (Retro) viruses generate DNA provirus (except HCV)

### Integration into cell chromosome

Introduction of new transforming gene:  
Viral oncogene (v onc)

Change in expression of protooncogene

*Activated*

Inactivation of tumor suppressor gene

e.g. p53

Inhibition of apoptosis

e.g. E6 Ag of HPV  
⊖ apoptosis of UV rays damaged cells

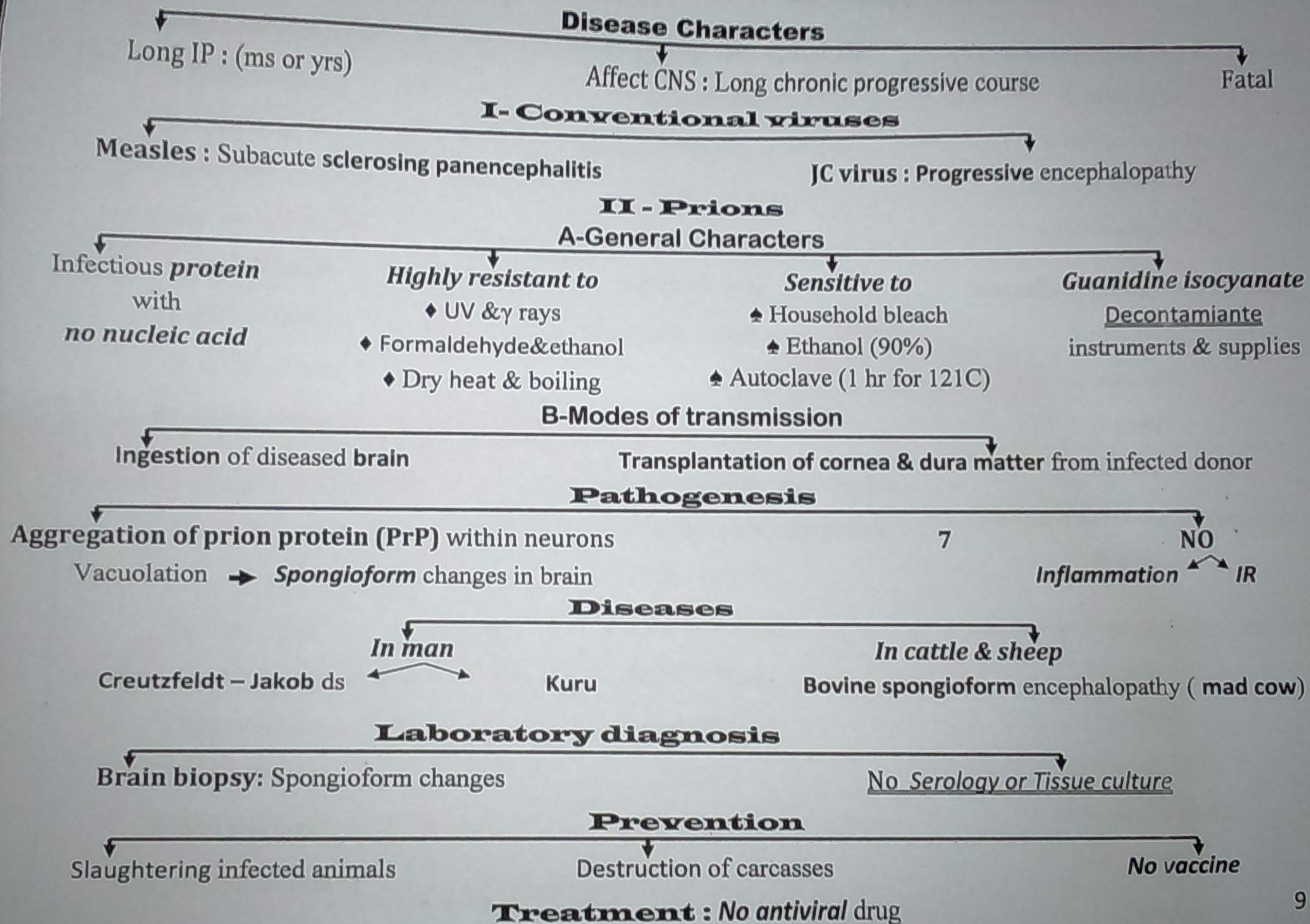
## Types of tumor viruses

Type	Family	Virus	Disease
I-DNA	A-Herpes	1-HSV 2	Cancer <u>cervix</u>
		2-EBV	♦ <u>Burkitt lymphoma</u> ♦ <u>Nasopharyngeal carcinoma</u>
		3-HHV 8	<u>Kaposi sarcoma</u>
	B-Papova	Human papilloma Virus	♣ <u>Genital tumor</u> ♣ <u>Laryngeal papilloma</u> <i>Benign</i>
	C-Hepadna	Hepatitis B	<u>Hepatocellular carcinoma</u>
	D-Pox	Molluscum contagiosum	<u>Molluscum contagiosum</u>
II-RNA	A-Retro	HTLV-1 Has <u>reverse transcriptase</u> → <u>DNA provirus</u> Integration	Adult <u>T cell leukemia &amp; Lymphoma</u>
	B-Flavi	Hepatitis C ( <u>No RT or provirus</u> )	<i>Chronic Inflammation</i> <u>Hepatocellular carcinoma</u>

*acute*



# Slow viruses & Prions





## Collective topics

### Viruses causing RTIs

- 1-Rhinoviruses.
- 2-Influenza viruses.
- 3-Parainfluenza viruses
- 4-Respiratory syncytial
- 5-Adeno viruses
- 6-Echo viruses
- 7-Coxsackie viruses
- 8-Corona viruses

### Viruses transmitted feco orally

- 1-Polio viruses
- 2-Coxsackie viruses
- 3-Echo viruses
- 4-Viruses causing gastroenteritis:
  - i.Rota viruses
  - ii.Calici viruses
  - iii.Astro viruses
  - iv.Adenoviruses 40&41

### Viruses causing encephalitis

- 1-Arbo viruses
- 2-HSV-1
- 3-Rabies virus
- 4-Measles virus
- 5-Rubella virus
- 6-Varicella Zoster virus

### Viruses causing aseptic meningitis

- 1-Enteroviruses (commonest causes):
  - i.Polio viruses
  - ii.Coxsackie viruses
  - iii.Echo viruses
- 2-Mumps virus
- 3-HSV-2

### Viruses transmitted by blood

- 1-HIV ,HTLV.
- 2-HBV,HCV,HDV.
- 3-CMV.
- 4-Parvovirus B-19.

### Sexually transmitted viruses

- 1-HIV ,HTLV.
- 2-HBV,HCV.
- 3-CMV.
- 4-HPV.
- 5-Molluscum contagiosum virus
- 6- HSV-2

### Vertically transmitted viruses

- 1-Rubella virus.
- 2-CMV.
- 3-HBV,HIV,HTLV.
- 4-Parvovirus B-19.
- 5-HSV-2&VZV.



## Essay Questions

### *Hepatitis & AIDS*

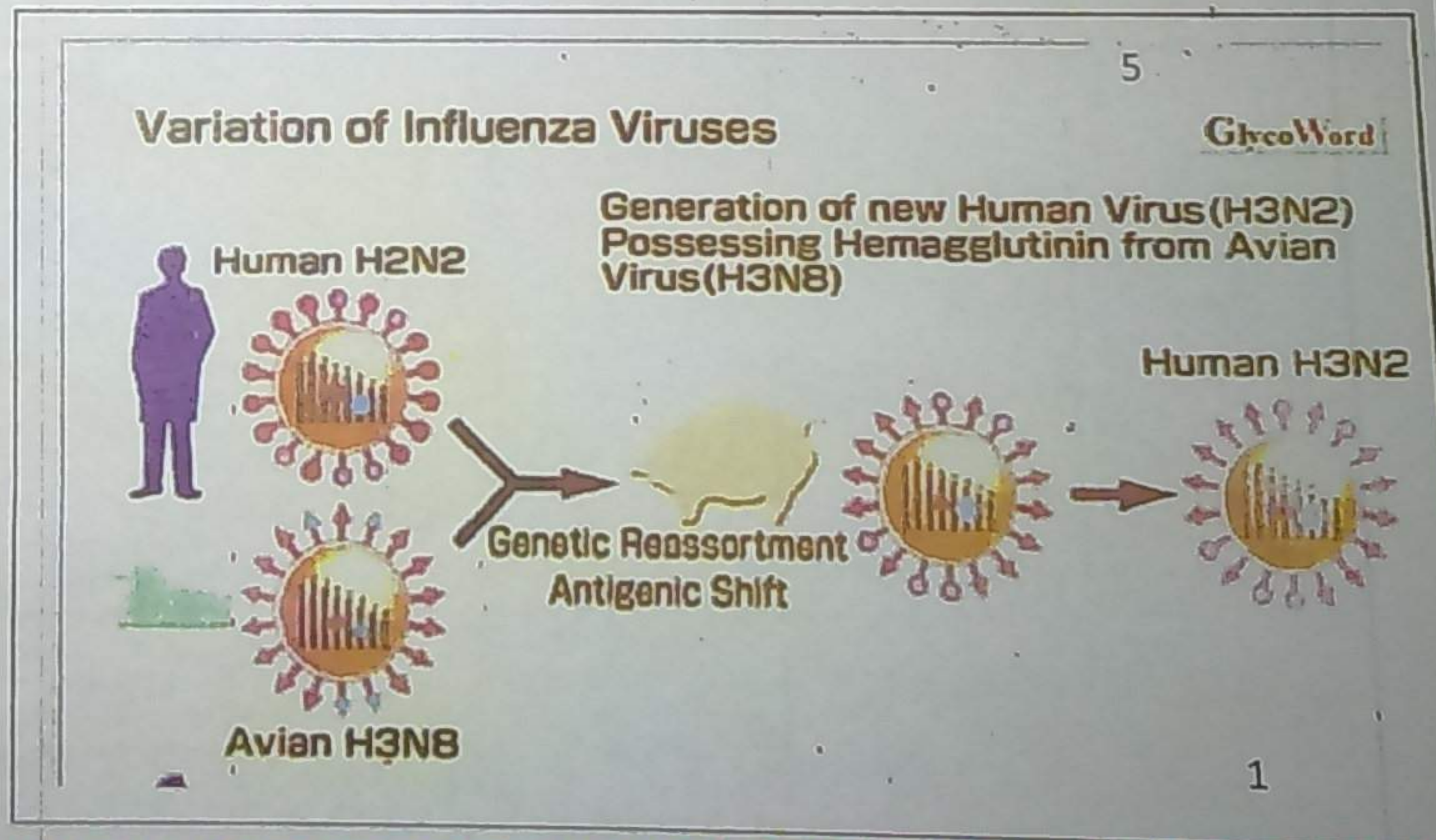
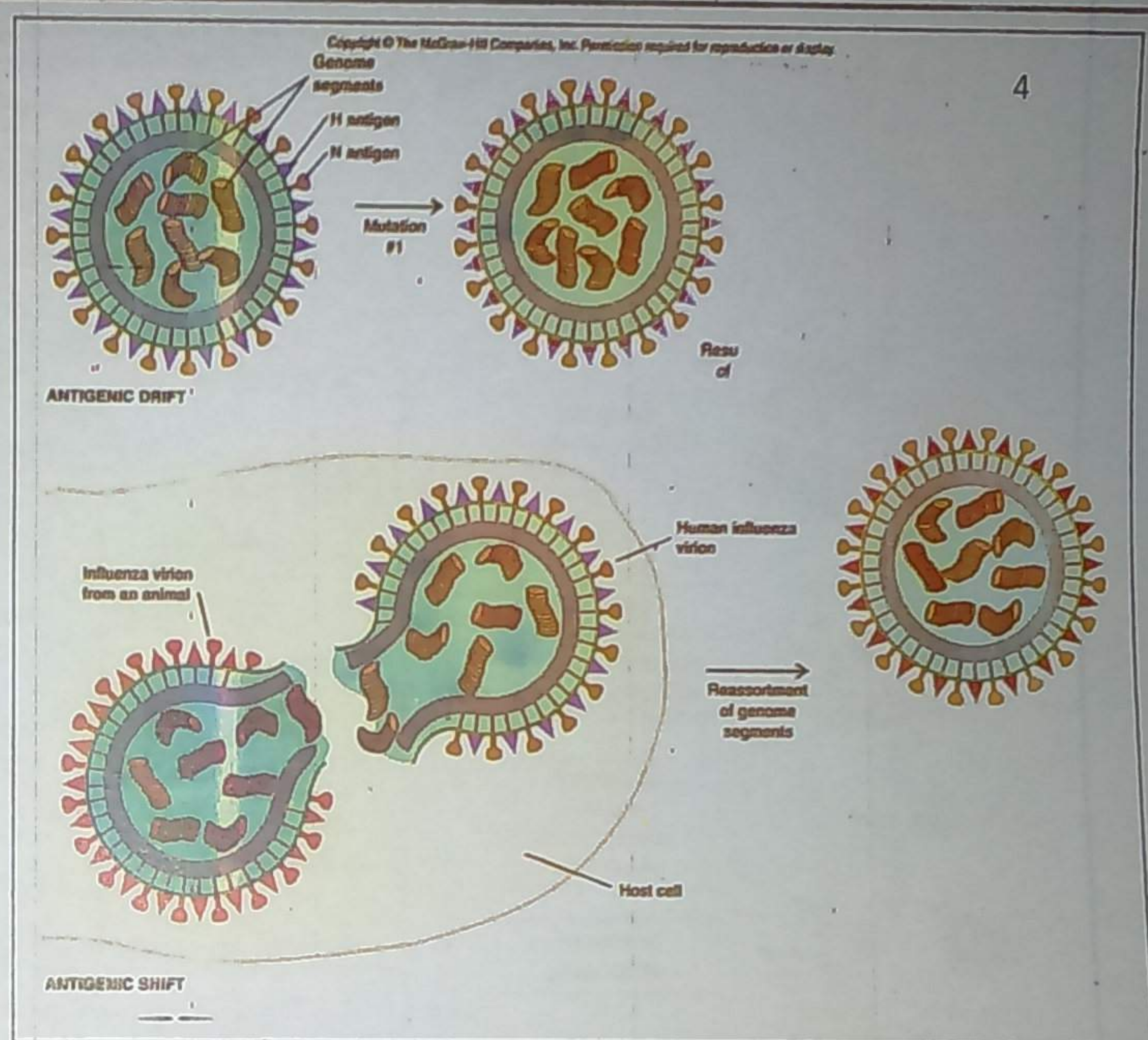
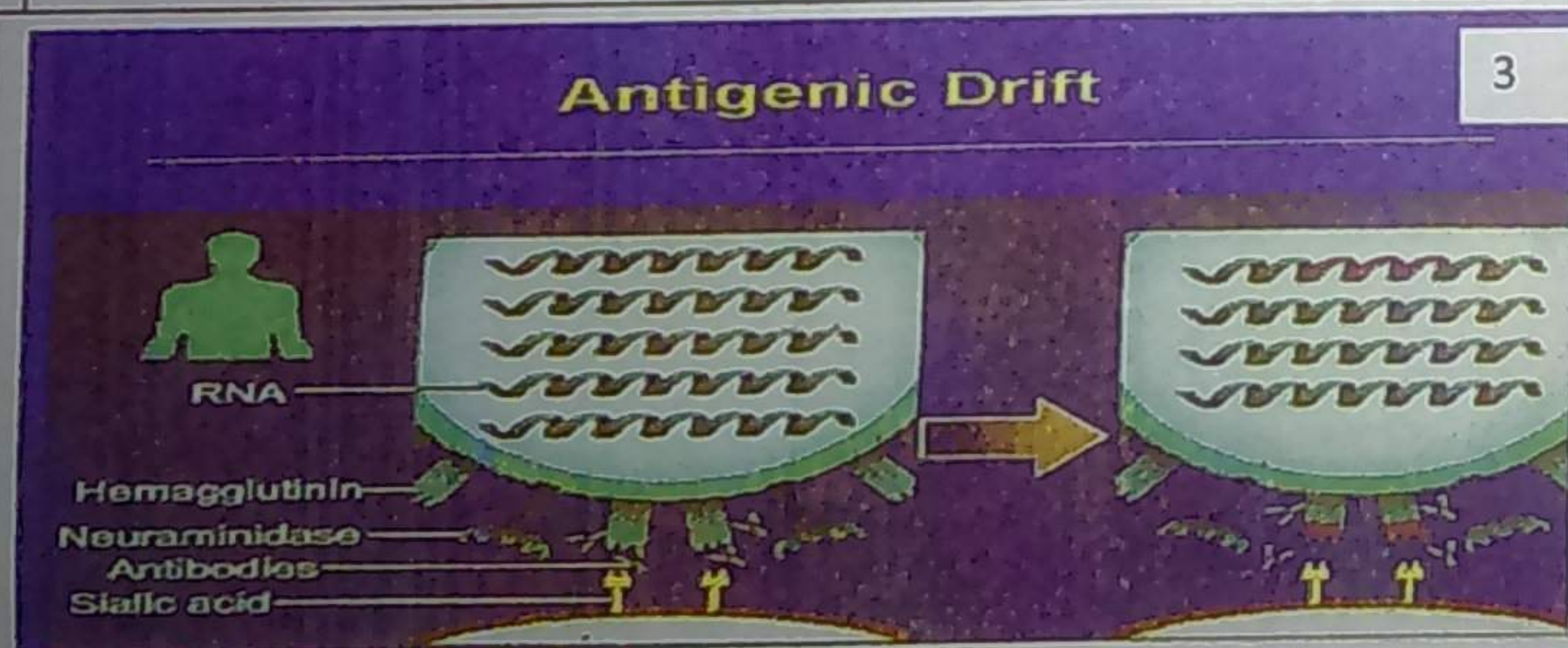
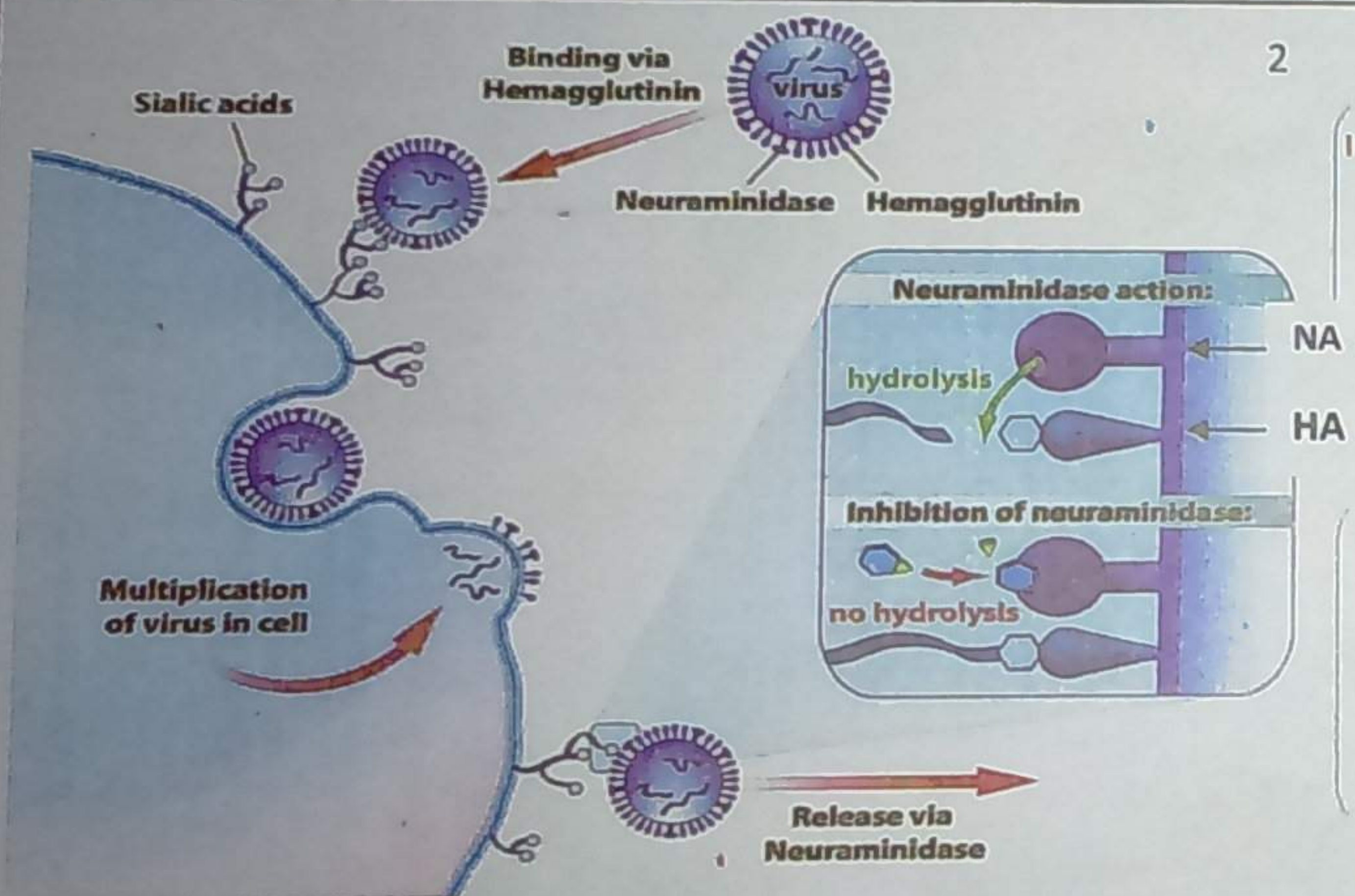
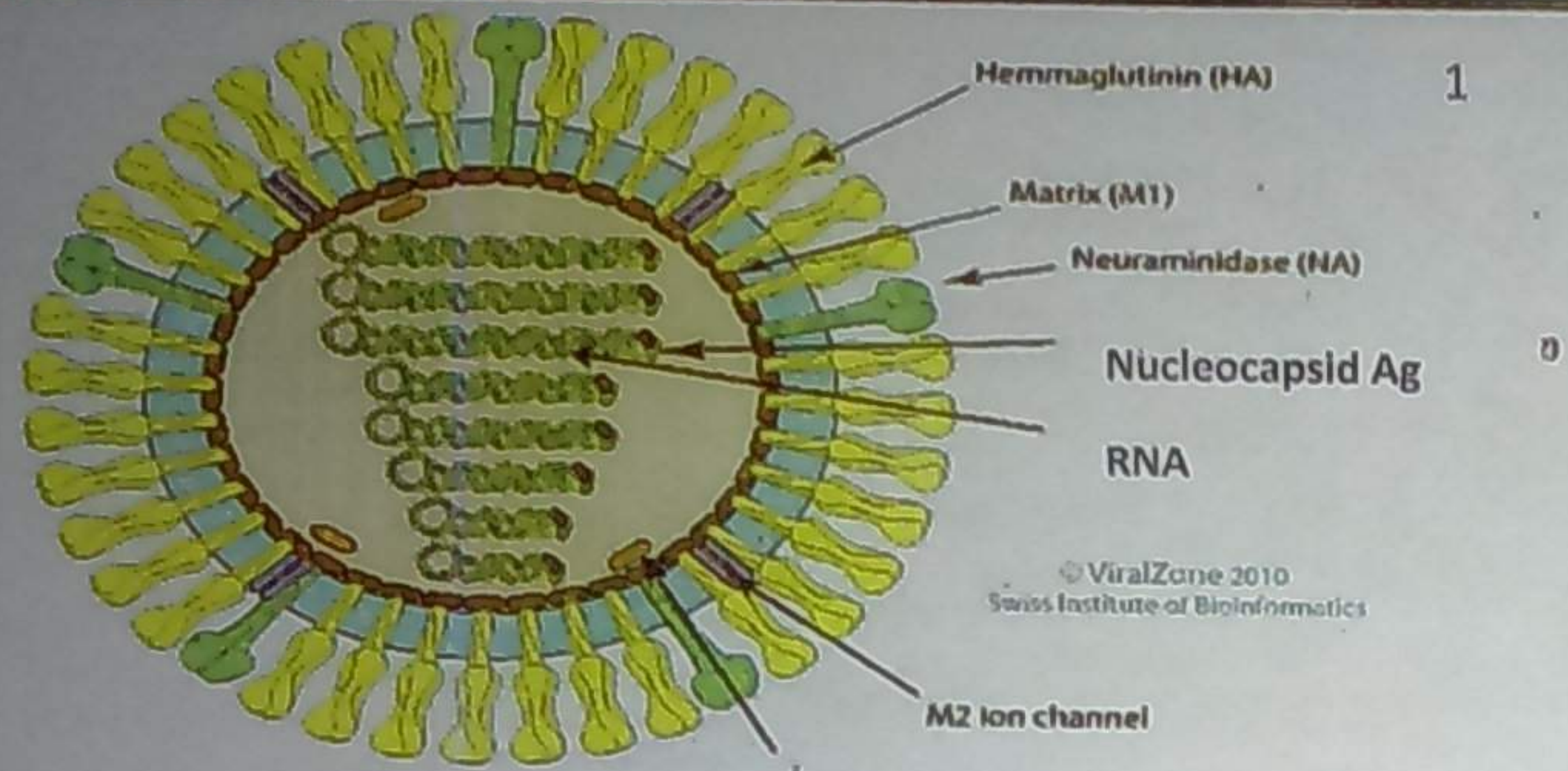
- 1-Diagnosis and prevention of hepatitis A.
- 2-Compare and contrast between Hepatitis A & B virus as regards general measures used in prevention and contents of vaccine for each
- 3-Enumerate serological markers of HBV infection & mention their significance.
- 4-Mention specific laboratory tests used in diagnosis of Hepatitis C virus and their significance  
(Don't mention liver functions tests or ELISA)
- 5-Discuss viral structure and laboratory diagnosis of HIV
- 6-Give reasons :
  - a.Failure to develop an effective vaccine against HIV
  - b.Hepatitis C infection is more dangerous than hepatitis A infection.
- 7-Enumerate antiretroviral drugs used in ttt of AIDS.
- 8-Mention the value of western blot technique in diagnosis of HIV.
- 9- Give a short account on novel ttt of hepatitis B



## *RNA Viruses & oncogenic viruses*

- 1-Compare and contrast between Orthomyxo and paramyxoviruses as regard genome antigenic variation.
- 2-Laboratory diagnosis and control of congenital rubella.
- 3-MMR vaccine.
- 4-Compare and contrast between CMV & rubella virus infection in pregnancy regarding critical time (CMV :throughout the whole pregnancy) and fetal outcome
- 5-Influenza chemoprophylaxis.
- 6-Give reasons : Influenza A virus undergoes antigenic Shift and drift.
- 7-Mention antigenic drift of influenza virus
- 8-Give reason : Antigenic shift occurs only in type A influenza virus.
- 9-Compare and contrast between mode of action of amantadine & acyclovir
- 10-Influenza viruses are classified into A,B &C serotypes.Explain the basis of this classification and mention 2 differences between between A &B serotypes.
- 11-Pathogenesis,CI P & diagnosis of corona virus
- 12-Laboratory diagnosis of RNA oncogenic viruses.
- 13 Mechanisms of cell transformation by oncogenic viruses
- 14-Give an account on human diploid vaccine of rabies.
- 15-Enumerate 2 arboviruses common in Egypt and their modes of transmission
- 16 Pathogenesis of viral hgic fevers and mention 3 examples
- 18-Laboratory diagnosis of rota virus infection
- 19-Define herd immunity and mention one vaccine that has this property
- 20-Give reason :
  - a.oral vaccine of polio is contraindicated in a feverish child.
  - b.Sabin vaccine is preferable in national preventive programs against poliomyelitis
- 21 Compare and contrast Salk and Sabin vaccine regarding preparation and route of administ.
- 22-Give reason :
  - a.it is hard to control diseases caused by rhinoviruses (multiple serotypes.....).
  - b.Human diploid vaccine has replaced crude nervous tissue vaccine in prevention of rabies.
  - c.Rubella virus causes teratogenic effect only if transmitted during 1<sup>st</sup> trimester.
- 23-Mention the causative agent & mode of transmission of :
  - a. German measles
  - b.Rift valley fever.
  - c.Dengue fever.







## Reverse Transcription

